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Poster

752. Modeling Disease with Induced Pluripotent Stem Cells

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 752.01/A1

Topic: A.03. Stem Cells

Support: SFB F44

Title: Generation and characterization of a human neuronal model of Spinocerebellar Ataxia Type 6 via induced Pluripotent Stem Cell differentiation

Authors: *C. BAVASSANO[1], A. EIGENTLER[1], R. STANIKA[2], S. BOESCH[3], R. NAT[1], G. DECHANT[1];
[1]Inst. for Neurosci., [2]Dept. of Physiol., [3]Dept. of Neurol., Med. Univ., Innsbruck, Austria

Abstract: Spinocerebellar Ataxia Type 6 (SCA6) is an autosomal dominant neurodegenerative disease characterized by late onset, slow progression and pure cerebellar ataxia. SCA6 is an allelic disorder associated with the CACNA1A gene, coding for the alpha 1 A (α1A) subunit of P/Q type voltage-gated calcium channel CaV2.1, which, in the brain, is particularly highly expressed in the cerebellum. SCA6 mutation consists of a short expansion of a polyglutamine stretch located in the cytoplasmic C-terminal tail of the channel protein. Extensive studies, both using heterologous expression systems and transgenic animal models, have highlighted the complexity of the pathogenic molecular mechanism of SCA6. Currently, the cause of the disease remains elusive, and no therapy is known for SCA6. We hypothesize that the analysis of patient-derived neurons expressing SCA6-CaV2.1 channels in their endogenous human neuronal microenvironment will help to shed light on the molecular cause/s of the disease. To this end, the aim of our study is to characterize the biophysical, cellular, and molecular properties of SCA6 patient-derived neurons differentiated from induced Pluripotent Stem Cells (iPSC). Control and SCA6 patient-derived iPSC were generated using Yamanaka´s reprogramming factors. Neuronal differentiation was achieved following a milestone-based protocol, and each stage of differentiation was defined by morphological criteria and the expression of stage-specific markers. In addition, a genetically encoded fluorescent reporter for the expression of the synaptic protein synapsin was used for the identification of mature neurons. The resulting SCA6 patient-derived neurons expressed the typical proteins of differentiated neurons, including cytoskeletal proteins (tau, MAP2, beta tubulin III), synaptic proteins (PSD95, synapsin, synaptophysin), voltage-gated ion channels (KV1.1, NaV1.1, NaV1.2), neurotransmitter-related enzymes and transporters (GAD67, VGLUT1, VGLUT2). Patch clamp recordings revealed the capability of firing action potentials and eliciting voltage-dependent calcium currents, and CaV2.1 channel

protein was expressed both in control and SCA6 neurons. The characterization of this human model includes the analysis of CaV2.1 currents, synaptic transmission, CaV2.1 channel protein subcellular distribution and differential gene expression, both in control and SCA6 neurons. In summary, we have generated functional SCA6 patient-derived neurons expressing the disease relevant protein via differentiation of iPSCs. This model will help to understand the effect of SCA6 mutation on CaV2.1 channel protein functionality in human neurons.

Disclosures: C. Bavassano: None. **A. Eigentler:** None. **R. Stanika:** None. **S. Boesch:** None. **R. Nat:** None. **G. Dechant:** None.

Poster

752. Modeling Disease with Induced Pluripotent Stem Cells

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 752.02/A2

Topic: A.03. Stem Cells

Support: Cedars-Sinai Medical Center, Regenerative Medicine Institute

Title: Banking and distribution of motor neurons derived from induced pluripotent stem cells: A focus on motor neuron diseases

Authors: *L. SHUE, B. SHELLEY, B. MANDEFRO, R. HO, L. ORNELAS, D. SAREEN, C. N. SVENDSEN;
Regenerative Med. Inst., Cedars-Sinai Med. Ctr., West Hollywood, CA

Abstract: There are many challenges involved in the production of valuable, consistent cell products that may be used to model diseases across different laboratories. We have addressed some of these challenges by creating a human induced pluripotent stem cell (iPSC)-derived motor neuron production core for disease modeling studies and translational work. In particular, we are focusing our efforts on producing banks of motor neurons derived from patients with motor neuron diseases such as amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA) using cutting-edge differentiation techniques for derivation and banking. We describe our banking and quality control methodology with a focus on batch-to-batch consistency. Key aspects to the process include: standard operation procedure development and implementation, barcoded sample and metadata tracking throughout the manufacturing process using custom inventory software, and rigorous purity, potency and identity assays. Alongside these differentiation protocol optimizations, we are also developing genome-wide methods to assay global mRNA and protein expression in these cells. These analyses aim to sensitively gauge

technical variability across batches, assess similarities to *in vivo* motor neurons, and detect biologically meaningful differences between disease and control conditions. Rigorous accounting of all these factors will be crucial for effective motor neuron disease modeling.

Disclosures: **L. Shue:** None. **B. Shelley:** None. **B. Mandefro:** None. **R. Ho:** None. **L. Ornelas:** None. **D. Sareen:** None. **C.N. Svendsen:** None.

Poster

752. Modeling Disease with Induced Pluripotent Stem Cells

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 752.03/A3

Topic: A.03. Stem Cells

Support: Cedars Sinai

Emulate Thereputics

Title: iBrain-on-a-Chip: a microfluidic platform to model neurodegenerative diseases using induced pluripotent stem cells

Authors: ***S. SANCES**[1], G. VATINE[1], C. LUCCHESI[2], S. J. KERNS[2], A. LAPERLE[1], C. HINOJOSA[2], G. HAMILTON[2], D. SAREEN[1], C. N. SVENDSEN[1];
[1]Cedars Sinai Med. Ctr., West Hollywood, CA; [2]Emulate Therapeut., Boston, MA

Abstract: Traditional tissue culture techniques for growing neurons and glia involve plating in a 2-D system with a large volume of static growth media. This is far from the normal environment of the living brain - in which the cells are within a three dimensional environment with limited extracellular space and high concentrations of extracellular matrix materials available to the cells. In order to mimic this environment, we have combined Organs-on-Chips technology with the proprietary iPSC differentiation protocols to more accurately model the *in vivo* environment. We have shown that we can successfully co-culture brain microvascular endothelial cells (iBMEC), neurons and astrocytes in a more physiologically relevant manner within the chip. The dynamic nature of the chip facilitates the creation of a more appropriate environment for growth and differentiation . The iBMEC, iMNs and astrocytes survived within the chips and differentiated appropriately. Astrocytes sent processes through the membrane pores to contact iBMECs in the adjacent channel. This model provides a unique platform to study the interactions between endothelial cells and neural tissue, forms the basis for a new Blood Brain Barrier-on-

Chip (BBB) model, and moves towards disease specific chip models using iPSCs derived from patients with ALS or Parkinson's disease.

Disclosures: **S. Sances:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate Therapeutics. **G. Vatine:** None. **C. Lucchesi:** A. Employment/Salary (full or part-time):; Emulate Thereputics. **S.J. Kerns:** A. Employment/Salary (full or part-time):; Emulate Thereputics. **A. Laperle:** None. **C. Hinojosa:** A. Employment/Salary (full or part-time):; Emulate Thereputics. **G. Hamilton:** A. Employment/Salary (full or part-time):; Emulate Thereputics. **D. Sareen:** None. **C.N. Svendsen:** None.

Poster

752. Modeling Disease with Induced Pluripotent Stem Cells

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Topic: A.03. Stem Cells

Support: NIH Grant 5T32MH073526-08

Title: Induced pluripotent stem cells to examine the c9orf72 repeat expansion in skeletal muscle

Authors: *E. SWARTZ, J. BAEK, M. PRIBADI, G. COPPOLA;
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Abstract: The hexanucleotide repeat (rGGGGCC) expansion in the gene C9orf72 is the most common cause of frontotemporal dementia (FTD), motor neuron disease (MND), and FTD/MND. Induced pluripotent stem cells (iPSCs) offer a way to explore the pathogenic mechanisms caused by specific genetic mutations in the tissues of interest. It is currently unknown how rGGGGCC impacts skeletal muscle in FTD/MND or whether skeletal muscle mimics pathology seen in motor neurons. As such, we sought to model rGGGGCC-related FTD/MND *in vitro* via reprogramming fibroblasts into iPSCs from (1) rGGGGCC carriers, (2) individuals diagnosed with sporadic FTD, and (3) healthy controls. We developed a novel protocol for differentiation of iPSCs into multinucleated, Myogenin positive skeletal muscle cells. We use this protocol to show that skeletal muscle derived from rGGGGCC carriers contain RNA foci, yet lack mislocalized TDP-43 and endogenous dipeptide repeat pathology. We additionally investigate acetylcholine receptor clustering, calcium release through internal ryanodine receptors, the presence of enlarged late endosomes, and the establishment of

functional neuromuscular junctions using complimentary iPSC-derived motor neurons seeded on opposing sides of microfluidic plates.

Disclosures: **E. Swartz:** None. **J. Baek:** None. **M. Pribadi:** None. **G. Coppola:** None.

Poster

752. Modeling Disease with Induced Pluripotent Stem Cells

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Support: Wellcome Trust ISSF Grant (No. 097819)

King's Health Partners

Royal Society UK

The Brain and Behavior Foundation (formally National Alliance for Research on Schizophrenia and Depression (NARSAD)).

Title: Subcellular localisation of schizophrenia susceptibility protein ZNF804A in human neurons

Authors: *P. M. DEANS, S. HALAI, P. RAVAL, K. WARRE-CORNISH, K. SELLERS, G. D. COCKS, J. PRICE, D. P. SRIVASTAVA;
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Abstract: Genome-wide association studies (GWAS) have been extensively used to identify candidate genes for schizophrenia. One of the first genetic variants achieving genome-wide significance for psychosis was rs1344706 in the zinc finger binding protein 804a (ZNF804a). The gene ZNF804a is highly expressed in the brain and encodes a protein of unknown biological function. The protein is predicted to contain a C2H2 zinc finger domain, suggesting a potential role in the regulation of gene expression through DNA and/or RNA binding. Consistent with this, functional knockdown of ZNF804a in human neural progenitor cells results in the dysregulation of cell adhesion molecules, suggesting a role in neural migration, neurite outgrowth and synapse formation. Critically, these cellular functions are thought to play a critical role in the emergence of schizophrenia. However, the biological function of this gene is currently unknown. In order to gain an insight into the biological function of the ZNF804a, we have studied the subcellular localisation of the protein in a range of neuronal cell types by

immunohistochemistry. Specifically, we have investigated the localisation of this protein in neurons differentiated from a human neural progenitor cell line (CTXOE16) and human induced pluripotent stem cells as well as in primary rat cortical neurons. ZNF804a was found to localise to the nucleus of neuronal progenitor cells, young developing neurons as well as in neurons with a mature morphology, consistent with a role in regulating gene transcription. Remarkably, ZNF804a could also be observed in the soma of neurons indicating an extranuclear localisation. Furthermore, the protein could also be observed in distal portions of MAP2 positive dendrites, where it colocalised with putative synaptic markers. Critically, in mature primary rat cortical neurons ZNF804a was found to localize to dendritic spines, the site of excitatory synapses, and to colocalise with synaptic proteins. These data are the first to provide a detailed characterization of the subcellular localisation of the ZNF804a protein in human neurons. The extranuclear and synaptic localisation of ZNF804a is consistent with a role for this protein in the regulation of RNA, and potential additional cellular functions.

Disclosures: **P.M. Deans:** None. **S. Halai:** None. **P. Raval:** None. **K. Warre-Cornish:** None. **K. Sellers:** None. **G.D. Cocks:** None. **J. Price:** None. **D.P. Srivastava:** None.

Poster

752. Modeling Disease with Induced Pluripotent Stem Cells

Location: Hall A

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Program#/Poster#: 752.06/A6

Topic: A.03. Stem Cells

Support: The Hartwell Foundation

Title: Illuminating neuroglia signaling with genetically encoded indicators of neural activity in a human stem cell model of Down Syndrome

Authors: *G. SHI[1], P. JIANG[1], S. PAPADOPOULOS[1], A. BHATTACHARYYA[2], J. WEICK[3], W. DENG[1], L. TIAN[1];
[1]biochemistry and molecular medicine, UC Davis, sacramento, CA; [2]Waisman Ctr., Univ. of Wisconsin, Madison, Madison, WI; [3]Dept. of Neurosci., Univ. of New Mexico, Albuquerque, NM

Abstract: Down syndrome (DS) is the most common genetic cause of mental retardation, influencing 1 in 700 newborns in the U.S. It remains largely unknown how genetic changes lead to altered neurocognitive growth in DS brain. To elucidate neural network development associated with DS pathogenesis, we have established an imaging platform based on genetically

encoded indicators of neural activity for functional modeling of the developing neural networks taking advantage of induced pluripotent stem cell (iPSC) technology. Through functional imaging of this model system, we described a hyper-calcium activity associated with DS specific astroglia, which presumably imposes cytotoxicity of co-cultured neurons including decreased synaptogenesis and dampened neuronal activity. These morphological alterations of neurons recapitulated those found in human postmortem tissues. We next dissected the molecular basis of abnormal astrocytic calcium homeostasis related to DS and discovered novel molecular targets involved in the altered neuron-astrocyte crosstalk. For example, DS astroglia displayed stronger response to mGluR5 agonists, which is consistent with higher mGluR5 expression. In addition, we found that overexpression of S100β, a calcium binding protein located on the chromosome 21, evokes spontaneous, hyper-calcium activity released by ER stores in DS astroglia. Selective knocking-down of S100β in DS astroglia abolished elevated spontaneous calcium activity and in turn rescued inhibited neuronal activity. This study demonstrated the logic of neuron-astrocyte crosstalk in directing neuronal network maturation and function underlying DS pathogenesis. It will enable an experimental platform from which other brain disorders leading to cognitive impairment may be similarly examined in human cellular models.

Disclosures: G. Shi: None. **P. Jiang:** None. **S. Papadopoulos:** None. **A. Bhattacharyya:** None. **J. Weick:** None. **W. deng:** None. **L. Tian:** None.

Poster

752. Modeling Disease with Induced Pluripotent Stem Cells

Location: Hall A

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Topic: A.03. Stem Cells

Support: Prechter Bipolar Research Fund

Steven M. Schwartzberg Memorial Fund

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A. Alfred Taubman Medical Research Institute

Title: Stem cell models of bipolar disorder

Authors: *A. J. WILLIAMS[1], C. J. DELONG[2], M. BAME[1], E. C. MARTINEZ[2], M. C. SMITH[3], R. DOUCETTE[3], M. G. MCINNIS[1], K. O'SHEA[2];
[1]Psychiatry, [2]Cell and Developmental Biol., [3]Univ. of Michigan, Ann Arbor, MI

Abstract: A major challenge in understanding human neuropsychiatric disorders has been the lack of viable cells and tissues for analysis. Patient-derived induced pluripotent stem cells (iPSC) now offer the opportunity to examine the full complement of neural tissues and the prospect of identifying underlying disease mechanisms. To study Bipolar Disorder (BD), we have derived and characterized iPSC from fibroblasts obtained from control (C) and patients with BD, and have differentiated them into neurons and glia. RNA from undifferentiated and differentiated iPSC were analyzed using microarray. Compared with the Allen Brainspan database, BD neurons have gene expression profiles most similar to 20-week brain whereas C were most similar to 16-week brain. Comparing microRNA expression in neurons between groups, 82 differentially expressed microRNAs were identified_many were mirtrons. We have also identified differences in neuronal lineage allocation between groups, with BD neurons favoring differentiation into ventral forebrain cells and C neurons forming dorsal cortical precursors. Because Shh signaling is responsible for ventral patterning of the CNS, and alterations in Hedgehog signaling pathway activity may reduce risk of developing BD, we examined expression of pathway members and the response of C and BD cells to Hedgehog pathway agonists, and observed increased responses in BD cells. We have also identified differences in calcium signaling in BD neurons, which are consistently more active than C neurons. Lithium pre-treatment significantly reduced calcium transients and wave amplitude in BD neurons, providing a tractable model system to examine the response of iPSC-derived neurons to pathway perturbagens and potential therapeutics. One of these is ketamine, which we are applying to iPSC-derived brain organoids to evaluate its effects on patterning and differentiation. Additional work examines the effects on CACNA1C expression associated with the AA genotype of rs1006737 -- the most replicated genetic risk factor for bipolar disorder -- in neuronal differentiation and function. We are also using CRISPR/Cas9 to edit BD cells with the AA genotype to the non-risk GG genotype, and assessing calcium signaling and differentiation potential. Finally, it is important to determine if our results are restricted to neurons. Co-culture of astrocytes and neurons may identify important differences in their behavior, or it is possible that both cell types are involved in BD. The overarching goal of our research is to identify novel disease phenotypes and mechanisms involved in bipolar disorder, with the ultimate aim of improving treatment.

Disclosures: **A.J. Williams:** None. **C.J. DeLong:** None. **M. Bame:** None. **E.C. Martinez:** None. **M.C. Smith:** None. **R. Doucette:** None. **M.G. McInnis:** None. **K. O'Shea:** None.

Poster

752. Modeling Disease with Induced Pluripotent Stem Cells

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: A.03. Stem Cells

Title: Aberrant DNA methylation in tumorigenic neural stem cells derived from human-iPS cells

Authors: *T. IIDA[1], A. IWANAMI[1], J. KOHYAMA[2], M. MATSUMOTO[1], H. OKANO[2], M. NAKAMURA[1];
[1]Dept of Orthop, Sch. of Med, Keio Univ., Shinjyuku-Ku Tokyo, Japan; [2]Dept of Physiology, Sch. of Med, Keio Univ., Shinjyuku-Ku Tokyo, Japan

Abstract: [Purpose] Recently, we have demonstrated the therapeutic potential of transplanting human induced pluripotent stem cell-derived neural stem/progenitor cells (iPSC-NS/PCs) for spinal cord injury (SCI) models in rodents and primates. However, we have found that some iPSC-NS/PCs' cell lines produce neurogenic tumors after transplantation (Nori et al, Stem Cell Reports 2015). Unfortunately, the tumors are not teratoma, and therefore, it is difficult to prevent the tumorigenesis even after excluding immature undifferentiated cells completely. The purpose of this study is to investigate the genomic alterations in iPSC-NS/PCs that may be related to cancer pathogenesis through DNA methylation analyses. [Method] Samples were prepared as follows: four iPS cell lines (253G1, 201B7, 836B3, 414C2) established in Kyoto University, and divided into two groups of iPSC-NS/PCs (tumorigenic cell lines (TC); 253G1-NS/PC & 836B3-NS/PC, and non-tumorigenic cell lines (Non-TC); 201B7-NS/PC & 414C2-NS/PC) based on our previous findings. Illumina Infinium® Methylation 450 Bead Chip were used to evaluate genome wide DNA methylation analyses of these iPSC-NS/PCs. [Result] Distinct differences in DNA methylation pattern were observed between the TC and Non-TC lines. Furthermore, some genes that had large differences of DNA methylation status between TCs and Non-TCs were involved in Wnt signaling & MAPK signaling- related cancer genes. Interestingly, the DNA methylation patterns were affected not only by the difference in cell lines but also by the difference in the passage numbers. [Conclusion] We have previously detected a difference in the expression levels of a specific gene between TC and Non-TC using transcriptome analyses (Nori et al, Stem Cell Reports 2015), but detailed mechanism of tumorigenicity remains to be unveiled. Here, we revealed a difference in DNA methylation pattern and difference in some genes' DNA methylation status, which may have some effects on tumorigenicity. These results enable us to establish criteria for quality control of iPS-NS/PCs in terms of their tumorigenicity.

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Poster

752. Modeling Disease with Induced Pluripotent Stem Cells

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Topic: A.03. Stem Cells

Title: A transcriptional comparison of human iPSC and mouse models of ALS defines the impact of motor neuron maturation, aging and disease

Authors: ***R. HO**[1], S. SANCES[1], G. GOWING[1], M. AMOROSO[2], J. O'ROURKE[1], A. SAHABIAN[1], H. WICHTERLE[2], R. BALOH[1], D. SAREEN[1], C. N. SVENDSEN[1]; [1]Cedars-Sinai Med. Ctr., Los Angeles, CA; [2]Columbia Univ., New York, NY

Abstract: Modeling neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) with human induced pluripotent stem cells (iPSCs) or with transgenic mice aims to reenact the embryonic development, maturation, aging, and subsequent degeneration of spinal motor neurons (spMNs). Several studies have reported molecular pathways affected by ALS conditions in both model systems as well as in post-mortem human spMNs. However, the extent to which these ALS models faithfully capture pathways observed in human spMNs has not been closely examined. Specifically, the maturity of human spMNs derived from iPSCs *in vitro* has not been directly compared to human spMNs *in vivo*, and whether a difference in maturity levels impacts faithful disease modeling has yet to be addressed. Furthermore, while transgenic mice have effectively modeled genetic forms of ALS, it is unclear to what extent this *in vivo* system faithfully captures all aspects of human spMN development and degeneration. Here, we compared global transcriptional profiles among human iPSC-derived spMNs, fetal and adult spinal tissues as well as orthologous tissues from mice. By comparing gene expression changes in ALS conditions across iPSC-derived spMNs, human spinal cord tissue and mouse spMNs, we highlight that iPSC and mouse ALS models affect some shared and some distinct pathways. Our comparative analysis among cells spanning embryonic to adult spMN states indicated that iPSC-derived spMNs are similar to fetal rather than aged adult spinal tissue. Additionally, gene co-expression network analysis identified gene modules that tightly associate with spMN fetal development, maturation, or aging. Interestingly, some of these modules enrich for clinical spMN disease genetic variants, revealing that maturation and age-related pathways may play roles in disease presentation. Collectively, these analyses suggest that more effective iPSC models of ALS necessitate strategies to further mature and age iPSC-derived spMNs. Lastly, we demonstrate that while the global expression of orthologous genes involved in spMN fetal development and maturation are largely parallel between human and mouse systems, only maturation but not fetal development gene co-expression networks are well-conserved between the two species. This analysis thus provides a more sensitive interrogation of gene-to-gene expression relationships underlying human and mouse spMN physiology. Overall, our findings support the idea that iPSC and mouse models of ALS are useful systems to study motor neuron

development and degeneration, but also highlight important differences that can guide more effective disease modeling.

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Poster

752. Modeling Disease with Induced Pluripotent Stem Cells

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Topic: A.03. Stem Cells

Support: Brain Korea 21 PLUS Project for Medical Science, Yonsei University

Title: Combined application of induced neural stem cell and gene therapy in stroke model

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Abstract: Objective: Recently, neural stem cell which is directly converted from human epidermal cell takes advantages in several ways. In addition to potential therapeutic effect of neural stem cell, gene therapy was combined to improve synergic effect on stroke disease. Vascular endothelial growth factor (VEGF) therapeutic gene under neuron-specific promoter can be inducible in induced neural stem cell (iNSC). Methods: After confirm the neural differentiation potential using several small molecules, plasmid containing neuron-specific enolase (NSE) promoter was transfected and cultured under normoxia or hypoxia conditions. After promoter activity was measured using luciferase, gene was replaced to VEGF. Results: Induced neural stem cell from human epidermal cells was differentiated into neuron. Luciferase assay revealed that neuron-specific promoter showed strong gene expression in iNSC. Moreover, iNSC transfected pNSE showed higher gene expression under hypoxia conditions mimic stroke disease *in vitro*. Replaced VEGF gene also showed high gene expression level under hypoxia conditions and with neuron-specific promoter *in vitro* and *in vivo*. Conclusion: iNSC has a great potential in cell therapy to treat neural degeneration disease. According to gene expression level, neuronal promoter showed strong activity in iNSC. Moreover, NSE promoter enhanced gene expression under hypoxia conditions. It indicates that applied cell and gene therapy represent a promising combined treatment in neural disease. Keywords: Induced neural stem cell, Neuron-specific promoter, Hypoxia, Vascular endothelial growth factor, Stroke model

Disclosures: **Y. Yun:** None. **J. Oh:** None. **J. Kim:** None. **Y. Ha:** None.

Poster

752. Modeling Disease with Induced Pluripotent Stem Cells

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Topic: A.03. Stem Cells

Title: Acidic fgf promotes neurite outgrowth of cortical neurons and improves neuroprotective effect in a cerebral ischemic rat model

Authors: *H. CHENG;
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Abstract: Acidic fibroblast growth factor (aFGF) is a neurotrophic factor which is a powerful neuroprotective and neuroregenerative factor for nervous system. Prior study had shown that the levels of FGFs significantly increase following ischemic injury, reflecting a physiological protection mechanism. However, few reports demonstrated the efficacy of applying aFGF in cerebral ischemia. A recent report showed that the intranasal aFGF treatment improved neurological functional recovery; however, it did not significantly reduce the lesion size in ischemic rats. The present study examines the neuroprotective effect of aFGF on cortical neuron-glial cultures under oxygen glucose deprivation (OGD)-induced cell damage and investigates whether epidural application of slow released aFGF could improve benefit on ischemic stroke injury in conscious rats. We used topical application of aFGF mixed in fibrin glue, a slow release carrier, over the peri-ischemic cortex and examined such treatment on cerebral infarction and behavioral impairments of rats subjected to focal cerebral ischemia (FCI). Results demonstrate that aFGF effectively protected cortical neuron-glial cultures from OGD-induced neuronal damage. Neurite extension from cortical neurons was significantly enhanced by aFGF, mediated through activation of AKT and ERK. In addition, topical application of fibrin glue-mixed aFGF dose-dependently reduced ischemia-induced brain infarction and improved functional restoration in ischemic stroke rats. Slow released aFGF not only protected hippocampal and cortical cell loss but reduced microglial infiltration in FCI rats. Our results suggest that aFGF mixed in fibrin glue could prolong the protective/regenerative efficacy of aFGF to the damaged brain tissue and thus improve the functional restorative effect of aFGF.

Disclosures: **H. Cheng:** A. Employment/Salary (full or part-time):; Taipei Veterans General Hospital.

Poster

752. Modeling Disease with Induced Pluripotent Stem Cells

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Topic: A.03. Stem Cells

Support: NIH Neurolincs Grant: 1U54NS091046-01

Title: Exploring electrophysiological properties of upper motor neurons and astrocytes in amyotrophic lateral sclerosis

Authors: *D. J. RUSHTON[1], G. M. THOMSEN[1], S. HOLLEY[2], G. G. GOWING[1], J.-P. VIT[1], O. SHELEST[1], P. SUEZAKI[1], M. LEVINE[2], C. N. SVENDSEN[1];
[1]Regenerative Med. Insitute, Cedars-Sinai Med. Ctr., West Hollywood, CA; [2]David Geffen Sch. of Med., UCLA, Los Angeles, CA

Abstract: We have recently shown that exclusive knock-down of mutant SOD1 (mSOD1) in the cortex of a mSOD1 rat model of amyotrophic lateral sclerosis (ALS) results in a significant delay in the onset of disease pathology and extended survival. This novel finding implicates the brain and upper motor neurons as important players in initiating the mechanisms that result in motor circuitry breakdown in ALS disease. Here, our work builds on this finding by exploring the mechanisms underlying the brain's involvement in ALS in both this rat model and human induced pluripotent stem cell (iPSC)-derived models. Our aim is to understand fundamental electrophysiological aberrations and elucidate their contribution to ALS pathology. We are investigating whether upper motor neurons exhibit altered function at different time points relative to disease onset in acute cortical slice cultures from the mSOD1 rat. Previous iPSC-derived models have studied lower spinal motor neurons and required primary rodent astrocytes to develop significant levels of excitability, but consistent with these models being of early developmental stages, studies have observed hyperexcitability. In order to assess the functional properties of developing neural cell types in ALS within the human context, we generated iPSC-derived upper motor neurons and astrocytes from ALS patient lines carrying the C9orf72 mutation. We are developing a co-culture system of both human disease and wild-type iPSC-derived upper motor neurons and astrocytes. The global aim of these related rodent and human studies is to provide a deeper understanding of excitability phenotypes in ALS in the cortical components of the motor circuit so that we can further elucidate the mechanisms involved in initiating the cascade of events associated with disease pathology.

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Poster

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Support: NIH NS078753

Autism Speaks

Angelman Syndrome Foundation

Title: Hyperexcitability in stem cell-derived neurons from Dup15q autism and Angelman syndrome patients

Authors: ***J. J. FINK**, T. M. ROBINSON, K. A. BOLDUC, E. S. LEVINE;
Neurosci., Univ. of Connecticut Hlth. Ctr., Farmington, CT

Abstract: Individuals with a duplication of the 15q11-q13 chromosomal region present with a neurodevelopmental disorder known as Dup15q, which represents the most common copy number variant associated with autism. In addition to the autistic-like symptoms such as intellectual disability and language delay, >50% of Dup15q patients suffer from some form of seizure disorder. Similarly, patients with maternal deletion of the same chromosomal region present with Angelman syndrome (AS), a related neurodevelopmental disorder in which a majority of the patients also develop seizures at some point in their life. Although the genetic cause of Angelman syndrome has been identified as the UBE3A gene, the specific gene or set of genes directly responsible for the Dup15q phenotype remains less clear, though UBE3A is thought to play an important role in Dup15q pathophysiology. Even less clear are the downstream UBE3A targets that might mediate these disease phenotypes, though several synaptic targets have been reported. Given the seizure phenotype associated with these disorders, we examined the excitability of neurons derived from Dup15q and AS patients using genomic reprogramming of human somatic cells into induced pluripotent stem cell (iPSC) lines. We have previously identified significant differences in resting membrane potential (RMP) and spontaneous synaptic transmission in neurons derived from AS patients compared to control

neurons, impairments that could cause hyperexcitability in these cells. For this reason, we measured these same properties in Dup15q neurons using electrophysiological and calcium imaging approaches. A 17-week electrophysiological characterization of 2 Dup15q patient lines and 2 control lines showed a more depolarized RMP at weeks 15-20 in Dup15q neurons, as well as alterations in the frequency and amplitude of spontaneous synaptic activity, similar to our findings in AS-derived neurons. Perhaps most interestingly, neurons derived from Dup15q patients also seemed to be more excitable than neurons derived from control subjects as measured by single-cell patch clamp recordings and population calcium imaging. Overall, these approaches may prove useful for identifying novel targets for drug discovery and for screening potential therapeutics aimed at reversing the seizures, movement disorders, and language and cognitive impairments in Angelman syndrome and autism.

Disclosures: J.J. Fink: None. **T.M. Robinson:** None. **K.A. Bolduc:** None. **E.S. Levine:** None.

Poster

752. Modeling Disease with Induced Pluripotent Stem Cells

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 752.14/A14

Topic: A.03. Stem Cells

Support: NIH Grant EY024940

BrightFocus G2012027

Title: Elucidating retinal ganglion cell development and disease modeling with human pluripotent stem cells

Authors: *S. OHLEMACHER[1], Y. XIAO[2], A. SRIDHAR[1], A. HOCHSTETLER[1], M. SARFARAZI[5], T. R. CUMMINS[2,3], J. S. MEYER[1,2,4];
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Abstract: The ability to derive retinal ganglion cells (RGCs) from human pluripotent stem cells (hPSCs) provides an unlimited supply of cells for the study of RGC development and disease, with important implications for drug screening, disease modeling, and cell replacement strategies. However, as this ability has been largely overlooked to date, the ability of hPSCs to yield a population of RGCs was explored in the current study. hPSCs were induced to

differentiate towards a retinal fate following previously established protocols and RGCs were subsequently characterized for the expression of RGC related features. Within 40 days of differentiation, RGCs could be readily identified due to the expression of RGC-associated markers as well as their documented transition through a highly enriched retinal progenitor stage. Analysis of hPSC-derived RGCs revealed that these cells expressed numerous morphological, phenotypical, and physiological characteristics of RGCs. In addition, skin fibroblasts were obtained from a glaucoma patient exhibiting an E50K mutation in the OPTN gene, and these fibroblasts were used to generate patient-specific OPTN iPSCs via mRNA reprogramming methods. OPTN iPSCs were differentiated to a retinal lineage in a stepwise fashion that allowed for the definitive identification of RGCs based upon gene expression patterns. Phenotypic differences between wild type and OPTN iPSC-derived RGCs were explored, including changes in golgi fragmentation, apoptosis, and autophagy. The data presented demonstrates the ability of hPSCs to serve as a reliable source of RGCs, including those derived from glaucoma patient sources, as seen by their ability to yield a population of cells possessing a full complement of RGC-associated characteristics. These results will facilitate future studies into the disease-related degeneration of RGCs and as such, will be instrumental as a tool for the study of optic neuropathies, as well as the development of future therapeutic approaches.

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Poster

752. Modeling Disease with Induced Pluripotent Stem Cells

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Topic: A.03. Stem Cells

Support: Commander's Innovative Research and Discovery Program, National Institutes of Health National Institute of Allergy and Infectious Diseases (IAA number AOD12058-0001-0000)

Defense Threat Reduction Agency – Joint Science and Technology Office, Medical S&T Division (grant number CBM.THRTOX.01.10.RC.021)

Title: A human pluripotent stem cell-derived neuron model as a functional assay for botulinum neurotoxin intoxication

Authors: *K. M. HOFFMAN, K. HUBBARD, P. BESKE, E. GLOTFELTY, J. GRYNOVICKI, P. MCNUTT;
MRICD, Aberdeen Proving Ground, MD

Abstract: Neurons derived from human pluripotent stem cells (hPSCs) have the potential to provide a physiologically relevant platform for investigating the human pathophysiological responses to chemical and biological threat agents. While in theory a networked population of *in vitro*-derived human neurons would combine the biological relevance of primary neurons with the flexibility of continuous cell lines, reproducible methods to generate synaptically active and electrically excitable human neurons have not been reported without the required presence of additional neural populations (i.e. primary neurons or astrocytes or implantation into the CNS). Therefore, we sought to develop conditions sufficient to generate functionally networked cultures of human stem cell-derived neurons (hSNs). Beginning with several hPSC lines, we used a variety of methods to derive hSNs and evaluated their morphological and functional characteristics out to 12 weeks. While most methods produced hSNs that exhibited unambiguous neurotypic markers and morphologies, the majority of cells lines failed to generate network activity and miniature post-synaptic currents. Transmission micrographs suggested that, in some cases, this failure was attributable to stalled presynaptic maturation. However, we did identify a combination of hPSC lines and differentiation methods that reliably produce mPSCs by 7 weeks, generating excitatory AMPA receptor-mediated currents (occurring at 0.1 - 1 Hz) that were eliminated by treatment with CNQX. In detailed studies, production of mEPSCs proved to be time- and density-dependent. Treatment with botulinum neurotoxin serotype A (BoNT/A), BoNT/B and tetanus neurotoxin (TeNT), which specifically block presynaptic release, resulted in cognate SNARE protein cleavage and eliminated mEPSCs, confirming that apparent synaptic activity resulted from synaptic neurotransmission and network activity. We are currently undertaking a detailed transcriptomic, morphological and functional characterization of synapse maturation and network behaviors in these lines with the goal of identifying developmental pathways that produce hSNs functionally appropriate for human neurotoxicological studies. Collectively, these data suggest that human-induced pluripotent stem cell-derived neurons may provide a physiologically relevant, synaptically active platform appropriate for the development of novel therapeutics for biological and chemical threat agents.

Disclosures: K.M. Hoffman: None. **K. Hubbard:** None. **P. Beske:** None. **E. Glotfelty:** None. **J. Grynovicki:** None. **P. McNutt:** None.

Poster

752. Modeling Disease with Induced Pluripotent Stem Cells

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: A.03. Stem Cells

Support: KAKENHI Grant No. 25870617

Title: Mislocalization of syntaxin-1 and impaired neurite growth observed in a human iPSC model for STXBP1-related epileptic encephalopathy

Authors: *S. YAMASHITA[1], T. CHIYONOBU[1], M. YOSHIDA[2], H. MAEDA[1], M. ZUIKI[1], S. KIDOWAKI[1], K. ISODA[2], M. MORIMOTO[1], M. KATO[3], H. SAITSU[4], N. MATSUMOTO[4], T. NAKAHATA[2], M. SAITO[2], H. HOSOI[1];
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Abstract: Objective: Syntaxin-binding protein 1 (STXBP1) is essential for synaptic vesicle exocytosis. Mutations of its encoding gene, STXBP1, are among the most frequent genetic causes of epileptic encephalopathies. However, the precise pathophysiology of STXBP1 haploinsufficiency has not been elucidated. Using patient-derived induced pluripotent stem cells (iPSCs), we aimed to establish a neuronal model for STXBP1 haploinsufficiency and determine the pathophysiologic basis for STXBP1 encephalopathy. Methods: We generated iPSC lines from a patient with Ohtahara syndrome (OS) harboring a heterozygous nonsense mutation of STXBP1 (c.1099C>T; p.R367X) and performed neuronal differentiation. Biochemical and morphological analyses were conducted on iPSC-derived neurons with STXBP1 mutation. Written informed consent was obtained from the parent and ethical approval for this study was obtained from the Review Board of Kyoto Prefectural University of Medicine and Kyoto University. Results: Both STXBP1 mRNA and STXBP1 protein expression levels of OS-derived neurons were approximately 50% lower than that of control-derived neurons, proving that OS-derived neurons are a suitable model for elucidating the pathophysiology of STXBP1 haploinsufficiency. Through western blot and immunocytochemistry assays, we found that OS-derived neurons show reduced levels and mislocalization of syntaxin-1, a component of soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins. In addition, OS-derived neurons have impaired neurite outgrowth. Significance: This model enables us to investigate the neurobiology of STXBP1 encephalopathy throughout the stages of neurodevelopment. Reduced expression of STXBP1 leads to changes in the expression and localization of syntaxin-1 that may contribute to the devastating phenotype of STXBP1 encephalopathy.

Disclosures: S. Yamashita: None. **T. Chiyonobu:** None. **M. Yoshida:** None. **H. Maeda:** None. **M. Zuiki:** None. **S. Kidowaki:** None. **K. Isoda:** None. **M. Morimoto:** None. **M. Kato:**

None. **H. Saitsu:** None. **N. Matsumoto:** None. **T. Nakahata:** None. **M. Saito:** None. **H. Hosoi:** None.

Poster

752. Modeling Disease with Induced Pluripotent Stem Cells

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 752.17/A17

Topic: A.03. Stem Cells

Support: KAKENHI Grant No. 15K09628

Title: Isogenic iPSCs from an individual with SCN1A mutation mosaicism revealed aberrant dopamine levels in Dravet syndrome neurons

Authors: *H. MAEDA[1], T. CHIYONOBU[1], M. YOSHIDA[2], S. YAMASHITA[1], M. ZUIKI[1], S. KIDOWAKI[1], K. ISODA[2], M. MORIMOTO[1], T. NAKAHATA[2], M. SAITO[2], H. HOSOI[1]; [1]Pediatrics, Kyoto Prefectural Univ. of Med., Kyoto, Japan; [2]Clin. Application, Ctr. for iPS Cell Res. and Application (CiRA), Kyoto Univ., Kyoto, Japan

Abstract: Background: Dravet syndrome (DS) is a severe childhood epilepsy typically caused by de novo dominant mutations in SCN1A, encoding for the voltage-gated sodium channel Nav1.1. Although DS is associated with severe cognitive and behavioral impairments, the precise pathophysiology of them has not been elucidated. There are wide phenotypic differences among individuals with SCN1A mutations, suggesting that the existence of genetic factors other than SCN1A mutation modify the phenotype. Additionally, as behavioral or cognitive disorders generally have subtle phenotypes *in vitro*, it is difficult to distinguish subtle disease-relevant phenotypic changes from unpredictable background-related variation. Therefore, well controlled cellular model system are required to improve our understanding of the mechanisms underlying DS. Methods: We generated induced pluripotent stem cell (iPSC) lines from an individual with SCN1A mutation mosaicism (Morimoto M, et al. Epilepsia, 2006) and separately cloned iPSC lines both with and without SCN1A mutation (DS and WT, respectively). These clones theoretically have the same genetic backgrounds, except for the SCN1A gene, and should serve as an ideal pair for elucidating the pathophysiology caused by SCN1A mutation. Then we performed *in vitro* neuronal differentiation. Written informed consent was obtained from the subject and ethical approval for this study was obtained from the Review Board of Kyoto Prefectural University of Medicine and Kyoto University. Results: The differentiated cells expressed the neuronal marker beta-III-tublin, and there was no prominent difference in the differentiation propensity between DS and WT cells. Quantitative RT-PCR and western blot

analysis revealed that both TH mRNA and TH protein expression levels of DS-derived neurons were higher than that of WT-derived neurons. Moreover, dopamine concentrations in media collected from DS-derived neuronal cultures, which were determined by ELISA, were higher than that from WT-derived neuronal cultures. Conclusion: This model enables us to investigate the neurobiology of DS throughout the stages of neurodevelopment. SCN1A mutation leads to changes in the dopamine system that may contribute to the behavioral abnormalities in DS.

Disclosures: H. Maeda: None. **T. Chiyonobu:** None. **M. Yoshida:** None. **S. Yamashita:** None. **M. Zuiki:** None. **S. Kidowaki:** None. **K. Isoda:** None. **M. Morimoto:** None. **T. Nakahata:** None. **M. Saito:** None. **H. Hosoi:** None.

Poster

752. Modeling Disease with Induced Pluripotent Stem Cells

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: A.03. Stem Cells

Support: Heinz C. Prechter Bipolar Research Fund

Steven M. Schwartzberg Memorial Fund

Joshua Judson Stern Memorial Fund

A. Alfred Taubman Medical Research Institute

Title: Investigation of the role of astrocytes in bipolar disorder

Authors: C. DELONG[1], E. MARTINEZ[2], M. BAME[2], A. WILLIAMS[2], L. AUGUSTAITIS[1], M. MCINNIS[2], *K. O'SHEA[1];
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Abstract: Bipolar disorder (BD) is a hereditary neuropsychiatric disorder characterized by extreme fluctuations in mood, alternating between mania and severe depression. The etiology of BD is thought to be neurodevelopmental, but it is not known what specific cell type(s) of the brain contribute to the condition. Numerous studies of postmortem brain samples from patients with neuropsychiatric disorder suggest that astrocytes may play a major role in the pathophysiology of these conditions. The directed neural differentiation of patient-derived induced pluripotent stem cells (iPSC) provides us with a developmental model to better understand the role of astrocytes in BD. Several iPSC lines from BD and controls were treated

via dual SMAD inhibition to induce neural differentiation, and maintenance of neural precursors as attached rosettes or suspended spheres in N2-containing medium resulted in an enriched population of dividing early astrocytes. Passaging and expansion in FGF-2 and EGF resulted in a population of which up to 99% were positive for the immature astrocyte marker CD44. CD44-positive cells were sorted by FACS and treated with ciliary neurotrophic factor (CNTF), which induced expression of the mature astrocyte-specific marker glial fibrillary acidic protein (GFAP). Currently, we are analyzing early and mature astrocytes for differences in gene and protein expression, as well as glialtransmitter release from mature astrocytes and measurements of oxidative stress.

Disclosures: **C. DeLong:** None. **E. Martinez:** None. **M. Bame:** None. **A. Williams:** None. **L. Augustaitis:** None. **M. McInnis:** None. **K. O'Shea:** None.

Poster

752. Modeling Disease with Induced Pluripotent Stem Cells

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Topic: A.03. Stem Cells

Support: NIH/NINDS Grant R21 NS089441

Tuberous Sclerosis Alliance Grant #332884

Human Genetics Institute of New Jersey

Finding A Cure for Epilepsy and Seizures

Title: Identifying neural cell phenotypes of Tuberous Sclerosis Complex using patient-derived stem cells

Authors: ***A. ZUCCO**[1], V. DAL POZZO[1], A. AFINOGENOVA[1], B. CROWELL[1], M. SHELDON[2,3], O. DEVINSKY[4], G. D'ARCANGELO[1,3];
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Abstract: Tuberous sclerosis complex (TSC) is a developmental disorder characterized by tumor susceptibility in multiple organs, brain malformations, and neurological manifestations. Despite considerable progress in understanding the genetic and signaling mechanisms underlying the

disease, effective treatments are still lacking, particularly with regard to the control of neurological symptoms such as epilepsy, autism, and intellectual disability. The most frequent genetic defects in TSC consist of heterozygous mutations in the TSC1 or TSC2 gene, leading to reduced expression of these proteins in all cells of the body. While loss of heterozygosity is sometimes observed in focal brain malformations or in lesions that develop in other organs, it is presently unclear whether this 'second hit' event is required to elicit neurological symptoms. At the molecular level, homozygous loss of TSC1 or TSC2 results in the activation of the rapamycin-sensitive mTORC1, a major growth-promoting mTOR-containing complex. This is because TSC1 and TSC2 proteins form a complex that inhibits mTORC1 by suppressing the function of the small GTP-binding protein Rheb, which is required for its activity. In the complete absence of either the TSC1 or TSC2 protein, mTORC1 is thus upregulated, promoting cell growth or proliferation through the phosphorylation of several cellular targets. However, the great majority of brain cells in TSC patients are heterozygous for TSC1 or TSC2 mutations, do not appear overgrown or dysplastic on pathological examination, and do not exhibit obvious upregulation of mTORC1 activity. Thus, it is not presently known whether or not they are abnormal. To help define the mechanisms of neurological disease in TSC, in this study we established induced pluripotent stem cells (iPSCs) from three sets of matched patients and sibling controls, and then derived neural stem cell (NSC) lines and differentiated neurons. These cell lines provided us with unprecedented insights into the cellular abnormalities that occur in the developing brain of TSC patients, and may facilitate the identification of new forms of treatments for these patients.

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Poster

752. Modeling Disease with Induced Pluripotent Stem Cells

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 752.20/A21

Topic: A.03. Stem Cells

Title: Establishment of the *in vitro* myelination model using human iPS cell-derived oligodendrocytes

Authors: ***T. YAMASHITA**[1], T. ONO[1], A. DOI[1], S. KOBAYASHI[1], Y. MIYAMOTO[2], J. YAMAUCHI[2], Y. BANDO[3], S. YOSHIDA[3], H. AOYAMA[1], T. ARAKI[1], Y. KATO[1], T. SHIRAKAWA[1], Y. SUZUKI[1], N. SATO[1], Y. KOGUCHI[1];

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Abstract: Oligodendrocytes myelinate axons to increase salutatory conduction and to regulate neural function. The disruption of interaction between neurons and oligodendrocytes causes a serious neural dysfunction categorized as white-matter deficits such as multiple sclerosis, Alzheimer's disease, depression, and autism. Neural dysfunction in these diseases is marked by biological complexity. In addition, species' differences exist in brain structure and myelin remodeling; therefore, the establishment of the *in vitro* myelination model from human cell source should be essential for elucidating the molecular mechanism of these diseases. Human pluripotent stem cell (PSC)-derived oligodendrocytes have a great potential to provide valuable sources for myelination studies. In our previous work, we have developed a proprietary single-cell and feeder-free (SFF) culture system for human induced pluripotent stem cells (iPSCs), which is a reliable platform to prepare several functional cells including oligodendrocytes. We herein establish cocultures using human iPSC-derived oligodendrocytes. We generated oligodendrocyte progenitor cells (OPCs) from human iPSCs maintained in the SFF culture within three months. These OPCs could be cryopreserved and initially enable to differentiate into O4-positive cells. And eventually, MBP-positive oligodendrocytes emerged in one month. Furthermore, we developed the *in vitro* myelination model. When the oligodendrocytes were cultured with neurons to be attached with axons, they were wrapped with glial cell plasma membranes. Collectively, the oligodendrocytes possess myelogenic potency in culture. Further investigation will be needed to expedite the establishment of this model which mimics human brain's physiological conditions. The *in vitro* myelination model using human iPSC-derived oligodendrocytes would substantially contribute to clarifying the physiological function and become the promising tool for drug discovery.

Disclosures: T. Yamashita: None. **T. Ono:** None. **A. Doi:** None. **S. Kobayashi:** None. **Y. Miyamoto:** None. **J. Yamauchi:** None. **Y. Bando:** None. **S. Yoshida:** None. **H. Aoyama:** None. **T. Araki:** None. **Y. Kato:** None. **T. Shirakawa:** None. **Y. Suzuki:** None. **N. Sato:** None. **Y. Koguchi:** None.

Poster

752. Modeling Disease with Induced Pluripotent Stem Cells

Location: Hall A

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Topic: A.03. Stem Cells

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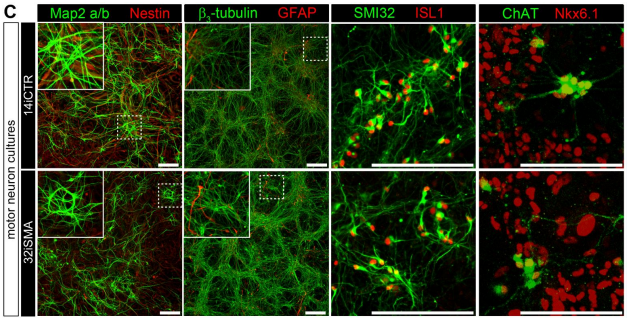
NIH/NCATS Grant UL1TR000124 (D.S)

NIH/NINDS Grant U54NS091046 (D.S)

Title: Dysregulation of neuronal development pathway proteins in stem-cell derived motor neurons from spinal muscular atrophy patients

Authors: *D. SAREEN[1,2,3], H. R. FULLER[4], B. MANDEFRO[1,3], S. L. SHIRRAN[5], A. GROSS[1], C. H. BOTTING[5], G. E. MORRIS[4];
[1]Board of Governors-Regenerative Med. Insititute, [2]Dept. of Biomed. Sci., [3]iPSC Core, Cedars-Sinai Med. Ctr., Los Angeles, CA; [4]Wolfson Ctr. for Inherited Neuromuscular Dis., RJAH Orthopaedic Hosp., Oswestry, United Kingdom; [5]5BSRC Mass Spectrometry and Proteomics Facility, Univ. of St Andrews, North Haugh, Fife, United Kingdom

Abstract: Spinal muscular atrophy (SMA) is an inherited pediatric neuromuscular disease characterized by degeneration of spinal motor neurons (MNs). SMN protein, the ubiquitously expressed SMN1 gene product mutated in SMA, specifically affects MNs via unknown mechanisms. Previously, patient fibroblasts and animal models were utilized to study the protein level consequences of reduced SMN. We derived human motor neurons (iMNs) from multiple individuals with SMA and healthy controls (CTR) by creating their induced pluripotent stem cells (iPSCs). Quantitative mass spectrometry on their iMNs revealed increased expression of 63 proteins in control iMNs compared to respective fibroblasts, whereas 30 proteins were increased in SMA iMNs versus their fibroblasts. Notably, UBA1 was significantly decreased in SMA iMNs, supporting evidence for ubiquitin pathway defects. Sub-cellular distribution of UBA1 was predominantly cytoplasmic in SMA iMNs in contrast to nuclear in control iMNs; suggestive of neurodevelopmental abnormalities. Additional proteins diminished in SMA iMNs were associated with neuronal development and differentiation including, βIII-tubulin and UCHL1. These neuron-specific consequences of SMN depletion were not evident in fibroblasts highlighting the importance of iPSC technology. The proteomic differences identified here will provide useful resource to explore the molecular basis of neurodevelopmental defects and develop novel biomarker therapeutic targets for SMA.



Disclosures: **D. Sareen:** None. **H.R. Fuller:** None. **B. Mandefro:** None. **S.L. Shirran:** None. **A. Gross:** None. **C.H. Botting:** None. **G.E. Morris:** None.

Poster

753. Development of Motor Systems

Location: Hall A

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Program#/Poster#: 753.01/A22

Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: CNPq

FAPEMIG

PRPq

ISN

Title: Impairment of motor behavior in young mice undergoing postnatal dopaminergic insult

Authors: ***B. R. SOUZA**[1,2], L. O. MATOS[1,2], L. O. GUARNIERI[1,2], G. S. PEREIRA[1,2]; [1]Univ. Federal De Minas Gerais, Belo Horizonte, Brazil; [2]Nucleo de Neurociencias, Belo Horizonte, Brazil

Abstract: Imbalance in dopamine-mediated neurotransmission, as well as neurodevelopmental abnormalities, are both features of schizophrenia and ADHD. Different neurodevelopmental windows are critical moments for the formation of the nervous system, such as the neuronal proliferation, differentiation and migration, synaptogenesis and pruning. It is well known that dopaminergic receptors are expressed in the developing brain and that dopamine plays an important role in the process of cell differentiation, migration and maturation. Thus, dopaminergic signaling might have diverse functions in the different developmental windows.

Studies using knockout animal models for dopaminergic receptors show behavioral changes in adult animals. However, it is impossible to know if the behavioral changes are consequences of the lack of the protein in the signaling process in the moment of the behavior, or if it is the consequence of the lack of the protein expression during the development. We have recently shown that dopamine regulates the development of GABAergic system and motor behavior in the zebrafish larvae. In this study, we hypothesized that early post-natal dopaminergic stress can affect the development of the brain and the emergence of motor behavior in young and adult swiss mice. To test this hypothesis, we injected levodopa intraperitoneally (10 mg/kg, 25 mg/kg and 50 mg/kg) for five days, from the day of birth until day 5 (P5). We investigated the motor behavior of young (4 weeks) and adult (8 weeks) mice by open-field test. We observed an increase of motor behavior in young females but not adult females and males. These results will help shape our understanding of the role of dopamine in brain development and provide new mechanistic insights for further assessing the neurodevelopmental origin model of neuropsychiatric disorders.

Disclosures: **B.R. Souza:** None. **L.O. Matos:** None. **L.O. Guarnieri:** None. **G.S. Pereira:** None.

Poster

753. Development of Motor Systems

Location: Hall A

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: Marie Curie IEF

ANR (ANR- 09- MNPS- 006), France

FRM (DEQ20110421301), France

Grant No 11.G34.31.0075, Government of the Russian Federation

Title: Sensory feedback by spontaneous twitches in the neonatal rat: spinal cord network dynamics

Authors: ***A. R. INACIO**[1], A. NASRETDINOV[2], J. LEBEDEVA[2], R. KHAZIPOV[1,3]; [1]INMED, INSERM UMR 901, Marseille Cedex 09, France; [2]Lab. of Neurobiology, Kazan Federal Univ., Kazan, Russian Federation; [3]Kazan Federal Univ., Lab. of Neurobio., Kazan, Russian Federation

Abstract: During the critical period for development of sensorimotor function, sleep is a predominant state, and behavior is dominated by spontaneous twitches, short contractions in atonic muscles. Twitches participate in activity-dependent formation of spinal cord circuits and trigger oscillatory patterns in the developing somatosensory cortex, delta-brushes in human fetuses and neonates, as well as spindle-bursts and early gamma oscillations in neonatal rats. It has thus been proposed that twitches originate sensory feedback, but this hypothesis has not been directly tested. By simultaneously recording neuronal activity at the population level across all spinal cord laminae and limb twitches and movements of neonatal rats, we demonstrate the following network dynamics: activity bursts in the ventral horn (motor) → twitching → dorsal horn activity (sensory). This phenomenon is disrupted following transection of sensory afferents: while bursts at the level of the ventral horn precede twitches and twitching frequency remains unaltered, activity at the level of the spinal dorsal horn is abolished. Our results provide direct evidence for twitches-triggered sensory feedback in activation of dorsal spinal cord neurons.

Disclosures: **A.R. Inacio:** None. **A. Nasretdinov:** None. **J. Lebedeva:** None. **R. Khazipov:** None.

Poster

753. Development of Motor Systems

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: NSF-RUI 0956598

NIH (OK-INBRE) 8P20GM103447

SWOSU

Title: Characterizing the Role of Beclin1/BEC-1 in Neurons of *C. elegans*

Authors: *A. POWERS, A. HOLGADO;
Dept. of Biol. Sci., Southwestern Oklahoma State Univ., Weatherford, OK

Abstract: For the past decades, scientists noted that many neurodegenerative disorders, such as Alzheimer's, Huntington and Parkinson 's disease are characterized by pathological accumulations of protein aggregates. More recently, analyses from brain autopsies and animals models show that the accumulation of toxic protein aggregates form with a reduced protein and macromolecule recycling machinery. Autophagy, the primary focus of the research summarized

herein, involves the removal of cell debris and the recycling of protein aggregates in health and disease. BEC-1, a Caenorhabditis elegans protein conserved from human to yeast, was shown to play an essential in autophagy and recycling of nutrients under starving conditions. Furthermore, recent research suggested that BEC-1 may link recycling of nutrients in nerve cells with maintenance of neurons. To test this probable link, we characterized the neuronal structure and function of *C. elegans* nematodes exposed to tissue specific bec-1 RNAi. In summary, animals expressing a double stranded RNA transporter in gabaergic motor neurons were treated with feeding bec-1 RNAi techniques and the phenotype of the tissue specific know down was evaluated. Collectively, we found that bec-1 knock down nematodes have developmental and functional defects at the level of motor neurons. Imaging analysis with epifluorescent microscopy revealed a reduction in the number of the D type motor neurons. Quantification of motor function showed varying levels of penetration of locomotion defects. Currently underway are studies of the effects of knocking down neuronal bec-1 under starving conditions.

Disclosures: **A. Powers:** None. **A. Holgado:** None.

Poster

753. Development of Motor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 753.04/A25

Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: NSF-RUI 0956598

NIH (OK-INBRE) 8P20GM103447

SWOSU

Title: Examining the link between axonal elongation and autophagy

Authors: ***L. VAN**, A. HOLGADO;
Dept. of Biol. Sci., Southwestern Oklahoma State Univ., Weatherford, OK

Abstract: Despite the wealth of information surrounding axonal elongation and guidance, autophagy, and cell survival, it is still unclear why neuronal components shown to work at the level of axonal outgrowth and cytoskeleton stability bind to components of the autophagy machinery. Moreover, it is undetermined why autophagy gene products, first characterized in yeast as Atg1, 6, 8, 9, 13, 18, are enriched in the nervous system of multicellular organism *C. elegans*. To shed some light into the intersection of autophagy in neurons and axonal extension,

herein, we present the research outcomes from investigations of three neuronal molecules: UNC-33, beclin1, and LK. The unc-33 gene encodes three conserved members of the CRMP/TOAD/Ulip/DRP family of proteins that includes mammalian CRMP2. Investigations of *C. elegans* UNC-33 isoforms demonstrated that these proteins mediate axonal guidance and axonogenesis in sensory, motor and interneurons. Beclin1 is the ortholog of yeast Atg6, a protein shown to regulate the lipid kinase Vps-34, and to promote formation of beclin1-Vps34-Vps15 core complexes, thereby inducing autophagy. In nematodes, BEC-1 (*C. elegans* homolog of vertebrate beclin1) is essential for survival, autophagy, and locomotion. LK is a brain metabolite and neurotrophic agent that according to our published and preliminary results binds to CRMP2, promotes axonal outgrowth, and induces the interaction of CRMP2-beclin1. In this study, we tested the hypothesis that the autophagic factor beclin1/BEC-1 and key neuronal molecules LK and UNC-33 control both autophagy and axonal elongation. We also investigated the role of neuronal autophagy in the context of UNC-6/Netrin mediated axonal guidance. By testing these hypotheses, we found that LK partially rescues the axonal elongation defects characterizing unc-33 mutants. Additionally, we determined that LK treatment enhances the expression of autophagy genes and the starvation induces expression of UNC-33. Lastly, analysis of the effects of autophagy on growth cone extrusion and repulsion is currently in progress. Together, these studies take us one step closer to the understanding of the link between autophagy and axonal elongation.

Disclosures: L. Van: None. **A. Holgado:** None.

Poster

753. Development of Motor Systems

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NIH OK INBRE 8P20GM103447

SWOSU

Title: Investigating the interplay of the axonal elongation protein unc-33/crmp and autophagy

Authors: *E. JANSING, A. HOLGADO;
Dept. of Biol. Sci., Southwestern Oklahoma State Univ., Weatherford, OK

Abstract: Collapsin response mediator proteins (CRMPs), are cytoskeletal adaptor molecules involved in a variety of normal cellular functions including alteration of cell shape and cell communication. UNC-33, the *C. elegans* CRMP, was first identified as a neuronal protein essential for axogenesis and axonal elongation. Since then, UNC-33 and the CRMP protein family have been associated with pathological disorders and neurological diseases. For instance, reports show that CRMP2 protein collects in cytoskeletal tangles in Alzheimer's disease, which may contribute to neural degeneration in this disorder. In other examples, differences in CRMP2 expression have been documented in some subsets of patients suffering paranoid schizophrenia. Lastly, the anticonvulsive drug lacosamide (VimPat) was found to act by binding to CRMP2, which unmasked an unknown function for CRMP2 in epilepsy. To further investigate CRMP mode of action in the nervous system, we continued with the characterization of unc-33 mutants and examined strategies for rescuing the mutant phenotype. Previous report from our laboratory demonstrated that lanthionine ketimine ester (LKE), a byproduct of aminoacid biosynthesis, partially rescue unc-33 mutants' axonal elongation defects. Herein, we describe that this rescue could be explained by an unknown mechanism that directly/indirectly stimulates the expression of genes involved in autophagy. Quantitative real time PCR result shows that genes atg-7, atg-18, bec-1, and lgg-1 are significantly induced in unc-33 mutant animals treated with LKE. Currently under work are analysis of the protein profiles of nematodes with defective or enhanced autophagy. Together this analysis leads us to determining the molecular mechanism underlying LKE effects on unc-33 mutants and the understanding of the bioactivity of LKE and its potential in therapeutics.

Disclosures: E. Jansing: None. **A. Holgado:** None.

Poster

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Support: NSF-RUI 0956598

NIH (OK-INBRE) 8P20GM103447

SWOSU

Title: Assessing the role of Autophagy in *C. elegans* neurons

Authors: *J. GREGSTON, A. HOLGADO;
Dept. of Biol. Sci., Southwestern Oklahoma State Univ., Weatherford, OK

Abstract: Macroautophagy (autophagy) is the process by which unneeded and damaged cellular components are catabolized and recycled. Autophagy begins with the formation of the phagophore, which encloses the targeted protein or damaged organelle forming an autophagosome. A lysosome then fuses with autophagosomes, breaking down and recycling the autophagosomal content. Autophagy plays an essential role in recycling cell materials needed for normal development, differentiation, and maintenance. Moreover, recent studies have shown that autophagy may degrade of Beta-amyloid plaques in the brain of patients suffering Alzheimer's disease. To gain more insights into the understanding of autophagy in neurons and it's potential role in normal and pathological conditions, we began monitoring autophagy induction in *C. elegans* neurons using a fluorescent LGG-1 protein. To this end, we first microinjected nematodes with the plasmid pAR-40.1 coding for LGG-1 fused to red fluorescent protein into animals expressing a green fluorescent protein (GFP) in D type motor neurons. Additionally, we crossed transgenic nematodes expressing LGG-1 fused to GFP with animals expressing a red fluorescent in D type motor neuron. Preliminary analysis of LGG-1 fused to GFP (LGG-1::GFP) demonstrates that we can monitor the induction of autophagy by measuring the density of the puncta of LGG-1::GFP as it lipidizes during autophagosome formation. Currently underway are experiments deciphering whether enhanced autophagy and recycling of cellular components aid in the rescue of nematodes defective in axonal pathfinding and elongation. Specifically, we are testing unc-51, unc-14, and unc-33, nematode mutant strains with aberrant axonal elongation defects and with homologs acting on a conserved autophagy pathway. Together this investigation is designed to test a potential link between autophagy and the development of proper neuronal circuitry in living multicellular organisms. Ultimately, understanding the bases of the interplay of autophagy in neurons will shed light into the workings of the nervous system in health and disease.

Disclosures: J. Gregston: None. **A. Holgado:** None.

Poster

753. Development of Motor Systems

Location: Hall A

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Program#/Poster#: 753.07/A28

Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Title: Exposure to ketamine during development heightens zebrafish growth spurt

Authors: *G. TORRES[1], J. R. LEHESTE[2];
[2]Biomed. Sci., [1]NYIT COM, Old Westbury, NY

Abstract: Ketamine is a dissociate anesthetic capable of inducing post-operative hallucination, psychosis and cognitive deficits in healthy individuals that bear an uncanny resemblance with those observed in schizophrenic patients. Yet, ketamine also appears to exert rapid and relatively sustained antidepressant-like effects in patients with major depression. Because ketamine is an antagonist of the N-Methyl-D-Aspartate (NMDA) ion-channel receptor, one of several subtypes of the glutamate receptor system, it is thought that derangements in glutamate neurotransmission may contribute to the pathophysiology of both schizophrenia and major depressive disorder. Previously, our laboratories provided behavioral and molecular evidence for the actions of ketamine using a new vertebrate model for psychiatric disorders: the zebrafish (Zakhary et al., Synapse 65: 160-167, 2011). Here, we provide further and new evidence for the actions of ketamine during vertebrate development. We document that zebrafish eggs exposed to sub-anesthetic doses of ketamine for 3-5 days post-fertilization, show a heighted somatic growth curve at 2 moths of development. These findings provide a cellular and molecular context to understand the consequences of prenatal ketamine exposure, and further support the use of zebrafish for understanding preclinical risk factors affecting candidate signaling pathways of psychological dimensions.

Disclosures: G. Torres: None. **J.R. Leheste:** None.

Poster

753. Development of Motor Systems

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Program#/Poster#: 753.08/A29

Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Title: Activation of distinct exploratory patterns by nicotine in larval zebrafish: evaluation of a novel testing methodology

Authors: B. CHEN, *F. M. SCALZO;
Bard Col., Annandale, NY

Abstract: The larval zebrafish is emerging as a useful model to assess neurobehavioral toxicity. A variety of behavioral assays have been developed to characterize normal behavior and the acute and chronic effects of several compounds. To date, such behavioral assays have been limited to relatively simple behavioral measures (e.g., swimming activity in a single well). The

present experiment describes methodology to assess exploratory behavior in 5 days-post-fertilization (5-dpf) larval TU zebrafish using a six-chamber, complex well-plate. In addition, the effect of acute nicotine exposure on exploratory activity in this complex environment was examined. Larvae were treated with either 0, 16.25 μM or 48.75 μM nicotine and were observed for 15 minutes. General Locomotor Activity, Zone Preference, Thigmotaxis (outer zone preference), Thigmotaxis Path Type, Chamber Transitions, and Latency to enter the Center Zone were measured using a Noldus tracking system. Larvae dosed with either 16.25 μM (2017±129) or 48.75 μM (2342±181) nicotine exhibited an increase in general locomotor activity relative to controls (1182±93). However, the pattern of locomotor activity was different between low and high dose nicotine. Larvae dosed with 16.25 μM nicotine exhibited more thigmotaxis coupled with an increase in overall exploratory behavior compared to controls, whereas the 48.75 μM larvae moved more than controls but did not exhibit a significant difference in thigmotaxis compared to controls. Both high and low dose nicotine treated larvae exhibited reduced latency to enter the center zone of more distant chambers than controls. These results demonstrate (1) the utility of this novel testing methodology in differentiating specific types of exploratory behavior, (2) that a low and high dose of nicotine increased exploratory behavior in a complex environment and (3) dose-dependent and time-dependent behavioral changes due to nicotine treatment suggesting altered control of a specific type of exploratory behavior. This study demonstrates a difference in the effects of low dose and high dose nicotine on larval zebrafish behavior and describes a new methodology that can be used to study complex behaviors in larval zebrafish.

Disclosures: **B. Chen:** None. **F.M. Scalzo:** None.

Poster

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Support: AHA Predoctoral Fellowship 15PRE22990027

NIH T32 EB009406

NIH RO1 NS058667

Title: Altered cortical thickness in pediatric hemiplegia

Authors: *R. L. HAWE[1], J. P. A. DEWALD[2];
[1]Physical Therapy and Human Movement Sci., [2]Northwestern Univ., Chicago, IL

Abstract: Pediatric hemiplegia results from a lesion occurring early in childhood. To date, research has focused on changes to white matter tracts in the brain, and largely ignored changes in cortical structures. However, subcortical lesions acquired during early development could potentially impact the cortical gray matter, by altering the course of development, or through degeneration or reorganization. Cortical thickness measures the distance between the pial surface and the border between grey and white matter. The developmental trajectory for cortical thickness has been established in typically developing children, and it has been shown to be a sensitive measure to changes in individuals with disorders including ADHD, autism, and schizophrenia. In this preliminary study, we use cortical thickness as a measure of cortical structural changes in children with lesions acquired early in development. Six participants (age 14.33 ± 8.87 years) with pediatric hemiplegia due to a prenatally or perinatally acquired subcortical lesion underwent magnetic resonance imaging using a MPRAGE sequence on a 3T scanner. FreeSurfer software was used to create cortical models and derive measures of cortical thickness. Average thickness measures were found for each sensorimotor Brodmann area, and percent differences between the lesioned and nonlesioned cortices were calculated for each participant. Cortical thickness was found to be increased on the lesioned side compared to the nonlesioned side across all sensorimotor regions. Brodmann areas 3a and 3b demonstrated the greatest increases in cortical thickness, with a 19.8% increase on the lesioned side. In typically developing children, sensorimotor cortices have an initial increase in cortical thickness followed by a steady decrease throughout development, which is associated with synaptic pruning and refinement. The relative increase in cortical thickness on the lesioned side compared to non-lesioned suggests that the subcortical lesion interfered with cortical development and normal activity-dependent pruning did not occur. The large differences seen in the sensory regions emphasize the need to look at both sensory and motor impairments in children with hemiplegia.

Disclosures: R.L. Hawe: None. **J.P.A. Dewald:** None.

Poster

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France-Israel High Council for Science and Technology

Title: A minimal neural mechanism for explorative behavior in songbirds and human babies

Authors: *R. DARSHAN[1,2], B. WOOD[2], S. PETERS[3], A. LEBLOIS[2], D. HANSEL[2];
[1]ELSC, Hebrew Univ., Jerusalem, Israel; [2]Lab. of Neurophysics and Physiol., Paris, France;
[3]Duke Univ., Durham, NC

Abstract: Motor behavior appears to be disorganized during early stages of development and is thought to be initially purely explorative. According to current theories, such exploration is essential for learning sensorimotor transformations. We combine data analysis and modeling to study the central neuronal mechanism that underlies explorative behaviors, focusing on babbling-like behaviors in human and non-human vocal learners. We quantify the temporal structure of babbling in four vocal learners with different levels of complexity in their adult vocalizations: zebra finches, swamp sparrows, canaries and human babies. We show that: 1) In all these learners, gesture duration distributions during early babbling are well fitted by a decaying exponential (in line with previous reports in zebra finches; Aronov et al., 2008) ; 2) interspecies differences in the temporal features of early babbling are to a large extent accounted for by time rescaling. These findings point to the existence of a central mechanism underlying explorative behavior which is common to all these learners and therefore robust with respect to anatomical and physiological differences between individuals and species. We investigate possible mechanisms for motor exploration in a theoretical model of the neuronal circuit that activates the effectors producing babbling in songbirds. It comprises a premotor and a motor network representing the avian cortical-like areas LMAN and RA, each consisting of a large number of excitatory and inhibitory spiking neurons. The premotor network projects to the motor network which in turn activates a small number of effectors as is the case in songbird anatomy. We argue that requiring the circuit to autonomously and robustly generate random activation of the effectors constrains its architecture and dynamics strongly. We show that this implies that: 1) the premotor as well as the motor area are recurrent networks operating in a regime where excitation and inhibition are balanced and 2) the feedforward projections from the former to the latter and then to the effectors are topographic. Under these conditions, the motor network exhibits temporally irregular firing with substantial correlations between neurons that activate the same effector. Importantly, correlations emerge from the recurrent dynamics of the circuit without any fine- tuning of parameters. When connected to a non linear model of a syrinx, the circuit generates explorative behavior with statistics similar to those exhibited in the data. Finally, we validate our theory by testing its predictions regarding the spatiotemporal patterns of activity in LMAN and RA in neuronal recordings in singing finches.

Disclosures: **R. Darshan:** None. **B. Wood:** None. **S. Peters:** None. **A. Leblois:** None. **D. Hansel:** None.

Poster

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: NIH Grant R00 DC012775-03

Title: Oculomotor nuclear organization in the larval zebrafish, Danio rerio

Authors: ***M. GREANEY**, D. SCHOPPIK;
New York Univ. Med. Ctr., New York, NY

Abstract: The oculomotor nucleus (nIII) comprises four of six motoneuron populations that innervate major muscles of the vertebrate eye. In adults, these populations are organized into spatially discrete subnuclei, suggesting a developmental origin with potential functional consequences. Developmentally, larval zebrafish (Danio rerio) ocular motoneurons form connections with particular extra ocular muscles ~3 dpf, and possess a functional vestibulo ocular reflex (VOR) by 4 dpf. Spatial organization of ocular motoneurons − or lack thereof − might provide clues as to how upstream vestibular neuron axons identify their appropriate downstream motoneuron partners. Here, we mapped nuclear organization of nIII motoneurons at two time points in early larval development: 5-7 dpf and 14 dpf. To target individual nIII subpopulations, we severed ocular motoneurons near their muscle attachment point. We then filled severed axons retro-orbitally with fluorophore-conjugated dextran crystals. We imaged dye-filled somata in the midbrain/hindbrain using a confocal microscope. By comparing the location of filled cells with the selective expression pattern of the islet1:GFP motoneuronal marker, we were able to classify many filled cells with respect to their target muscle (n=2171, 5-7dpf; n=344, 14dpf). We identified a spatially contiguous cluster of motoneurons innervating the contralateral superior rectus (SR), that by 5 dpf was positioned ventromedially within nIII and remained so at 14dpf. At both time points, we found slight overlap between this cluster and neurons of the other three oculomotor populations: medial rectus (MR), inferior rectus (IR), and inferior oblique (IO). In contrast, at 5-7 dpf, we observed MR, IR, and IO somata scattered throughout nIII. Initial findings in 14 dpf fish suggest that IR and MR neurons occupy most of dorsolateral nIII at this stage, with IR possibly more rostral than MR, while IO neurons cluster at the lateral edge of ventral nIII. Finally, we identified the superior oblique (SO) motoneurons that

comprise the trochlear nucleus (nIV) just caudal to the midbrain-hindbrain boundary. We conclude that the aggregation of superior motoneuron populations (SR/SO) concludes by 5 dpf. In contrast, aggregation of the MR/IR/IO motoneurons into subnuclei must occur later in development. Intriguingly, our data suggest that functional innervation of target extraocular muscles is complete by 5 dpf. Further, the ability of larval fish to perform a VOR suggests that upstream vestibular projections are similarly functional. Ongoing work aims to collect functional data from motoneurons executing the VOR while fish experience a vestibular stimulus.

Disclosures: **M. Greaney:** None. **D. Schoppik:** None.

Poster

753. Development of Motor Systems

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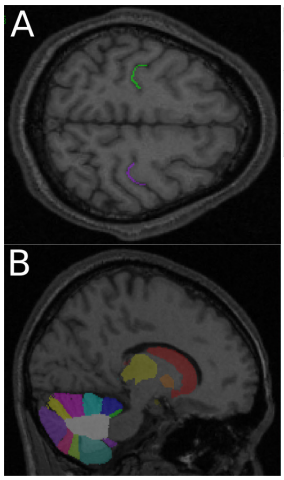
Title: From M1 to Cerebellum: What effect does hand-preference have one the local volumes of motor related structures?

Authors: ***J. GERMANN**[1], R. PATEL[1], G. A. DEVENYI[1], M. M. CHAKRAVARTY[1,2,3]; [1]Cerebral Imaging Centre, Douglas Mental Hlth. Uni, Verdun, QC, Canada; [2]Dept. of Psychiatry, McGill University, Montreal, QC, Canada; [3]Dept. of Biomed. Engin., McGill University, Montreal, QC, Canada

Abstract: People preferentially choose one of their hands to perform tasks and there is a strong bias towards dominance of the right hand (90% of population). This bias develops early and is

stable throughout the lifetime. Is this hand preference associated with asymmetries throughout the brain regions associated with motor control? MRI images of the brains of 17(6f) right handers (RH) and 14(7f) left handers (LH) were used. To estimate the extent of the hand area of M1 the sulcal ribbon along the hand-knob was manually labelled. Volumes of the Basal Ganglia, Thalamus and Cerebellar Regions were extracted for all individuals using MAGeTBrain a multi-atlas based automated segmentation tool. The central sulcus shows a strong significant asymmetry ($p<.05$). The sulcal region (depth x length) of the hand is 12% larger in the left in RH and 40% larger on the right in LH. The basal ganglia unexpectedly showed large variation and no significant results. A trend was found in the thalamus ($p<.1$). The relative (left vs right) size of the right thalamus increases in LH. The results of the cerebellar regions were surprising. A strong significant effect was found showing that RH have a larger cerebellum bilaterally ($p<.003$) most pronounced in the Crus I regions. Two possible processes might be involved in the local volume differences demonstrated in this study: plastic changes associated with practise and differences in neuronal development that give rise to hand preference. The strong effect found in the M1 region combined with findings that training has a marked effect on regions of the motor cortex leads us to believe that life-long practice and brain plasticity is at work here. The strong effect found on general cerebellar volume though is most likely an indication for a deviation from “normal” early in development that causes both, smaller cerebellar volumes and left-handedness. Our results suggest that hand preference and associated local volume differences might not only reflect differences in motor behavior but are also caused by the genetic/developmental processes involved in determining hand preference.



	Left-handers	Right-handers
Left primary hand area (mm^2)	450	558
Right primary hand area (mm^2)	630	494
Total cerebellar (mm^3)	166653.8	177460.4

A shows the manual segmentation of the central sulcus hand area in an individual subject. The area of the sulcal ribbon drawn along the hand-knob was used for analysis. **B** shows the segmented subcortical and cerebellar areas using MAGeT in the same individual. The table above summarized the most prominent significant results: The hand area shows strong asymmetry with the dominant hand having a larger area. This asymmetry is reversed in LH.
RH have a larger Cerebellum!

Disclosures: **J. Germann:** None. **R. Patel:** None. **G.A. Devenyi:** None. **M.M. Chakravarty:** None.

Poster

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: BMBF 01GQ1407

NIDCD 1R01DC014368

Title: Changes in swimming parameters during the development of Xenopus tadpoles

Authors: *S. HÄNZI[1,2], L. HOFFMAN[3], M. PAULIN[4], H. STRAKA[2];
[1]Grad. Sch. of Systemic Neurosciences, Planegg, Germany; [2]Dept. Biol. II, Ludwig-Maximilians-University, Munich, Germany; [3]Dept. of Head & Neck Surgery, Geffen Sch. of Med. at UCLA, Los Angeles, CA; [4]Dept. of Zoology, Univ. of Otago, Dunedin, New Zealand

Abstract: Morphological changes during ontogeny are often associated with alterations in physiological parameters such as locomotor performance, dynamics and behavioral repertoire. Amphibian development is a particularly good example, where the maturation and improvement of the undulatory tail-based swimming during progressive larval development is succeeded after metamorphosis by a limb-based locomotor pattern in adult frogs. Moreover, any change in locomotor performance or strategy requires a concurrent adaptation of the vestibular system for appropriate neuronal encoding of the motion profile generated by the locomotion. Here, we studied the swimming behavior of Xenopus laevis tadpoles, and examined whether the morphological changes of the larval body plan are accompanied by concurrent changes in locomotor parameters and behavioral adaptations. High-speed video images (up to 200 frames/s) of swimming sequences were captured at different developmental stages of larval (stage 47-59) and young adult frogs (stage 61). The swimming trajectory of young larvae (stage 47-49) essentially covered most of the tank area. In contrast, older larvae (> stage 53) and adult frogs showed thigmotaxis represented by locomotor trajectories that generally followed the walls of the tank. This change in swimming pattern correlated with the progressive bilateral outgrowth of touch-receptive tentacles in older larvae and reflects a behavioral adaptation of the larval life style, even though the two appendages disappear after metamorphosis. The growth of the larvae was also accompanied by an increase in forward locomotor speed and head angular velocities during undulatory swimming. These changes were reflected in the statistics of head kinematics extracted from sequences of free swimming. For instance, peak angular head velocities reached several hundred degrees per second during fast undulatory swimming. These measures provide more naturalistic representations of head motion profiles exhibited by these animals that will serve to establish naturalistic stimuli for probing vestibular responses and neuronal computation underlying sensory-motor transformation in peripheral and central circuits. Moreover, the high

frequency and velocity components of the locomotor profile suggests the presence of neuronal elements in the vestibular system with coding capabilities that ensure faithful neural representation of the respective kinematic components.

Disclosures: S. Hänzi: None. **L. Hoffman:** None. **M. Paulin:** None. **H. Straka:** None.

Poster

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: KAKENHI 15H01587

Title: Orexinergic modulation on the cervical network regarding the fetal movement using rat brainstem-spinal cord preparation

Authors: *A. ARATA[1,2], H. SHIMOMURA[3], M. ITO[2], A. NISHIYAMA[2], Y. TAKESHIMA[3], A. YAMANAKA[4];
[2]Dept. of Physiol., [3]Dept. of Pediatrics, [1]Hyogo Col. of Med., Nishinomiya, Japan; [4]Dept. of Neurosci. II,, Res. Inst. of Envrn. Medicine, Nagoya Univ., Nagoya, Japan

Abstract: Orexin system is particularly important for maintenance of wakefulness because orexin deficiency results in narcolepsy. In late fetal stage, fetal movement in sleep begins to be synchronous with rapid eye movement, and this state is called the prototype of REM sleep. In neonatal REM stage, it is known that the exciting system in spinal cord such as locomotion is inhibited. We would examine the role of orexin in the relationship between fetal movement and REM sleep. In fetal rat isolated brainstem-spinal cord preparation, our previous study already reported two kinds of activities recorded from 4th cervical nerve root (C4); one is respiratory activity that is comparatively rhythmic activity corresponding to phrenic nerve activity, and the other is non-respiratory activity (NRA) which is not rhythmic, accompanied by high amplitude, and that was corresponding to the fetal movement. Additionally in after birth, we could not observe the NRA, but the similar activity as NRA was induced by strychnine application (Shimomura et al, 2015). The critical point of the disappearance of NRA existed at E19-20 and NRA was abolished by application of an antagonists of strychnine-insensitive glycine binding site on the NMDA receptor. The NRA was controlled by the excited glycine via NMDA receptor glycine binding site and by the inhibition via Cl-channel related glycine receptor. Orexin depressed the NRA and potentiated respiratory activity. On the other hand, application of

strychnine showed increase of respiratory rate and showed no alteration of NRA. The increase of orexin level induced the NRA inhibition. After removal of brainstem from this preparation, NRA still existed but decreased the frequency. NRA in the spinal cord was also depressed by orexin. In fetal stage, orexin might modulate inhibitory system in the cervical circuit, and also might modulate formation of wakefulness and REM sleep.

Disclosures: **A. Arata:** None. **H. Shimomura:** None. **M. Ito:** None. **A. Nishiyama:** None. **Y. Takeshima:** None. **A. Yamanaka:** None.

Poster

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Title: Lipopolysaccharide-induced IL-6 and TNFalpha expression in neonatal rat nucleus tractus solitarii (NTS)

Authors: J. CLAY, M. CUSTER, R. JOHNSON, *C. G. WILSON;
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Abstract: Lipopolysaccharide (LPS), or endotoxin, is commonly used to induce an inflammatory response in animal models. In premature infants, systemic infection (sepsis) causes tachypnea and an increase in the number of apneas over time but the mechanism by which sepsis alters breathing control is unknown. Our laboratory has previously shown that LPS instilled into the trachea of neonatal rats causes changes in IL-1beta expression in brainstem regions associated with breathing control_including the rostral medulla, nucleus tractus solitarii (NTS), and the hypoglossal (XII) motonucleus. We hypothesize that increased expression of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFa) are upregulated in the rostral ventro-lateral medulla (RVLM) and NTS after injection of LPS into the trachea and these changes are correlated with dysregulation of breathing. To test this hypothesis, we performed immunohistochemistry on brainstems harvested from 10 to 12 day old rat pups (Sprague-Dawley) two hours after injection of LPS (0.5 mg/kg in 10 microliters of saline) into the trachea. Breathing pattern was monitored via diaphragm EMG during the LPS injection and recovery from surgery. We cut brainstems using a cryostat (20 micron sections) and acquired sections that included RVLM, XII, and the NTS. We performed overnight immunohistochemistry runs to label IL-6 and TNFa. We acquired images of the sections using a Zeiss upright microscope and all images were analyzed using a custom ImageJ plug-in to identify and count the stained cells.

We saw that the RVLM and NTS had an increase in IL-6 and TNFa expression when compared to sham surgery and control animals. IL-6 was 33.0% ($p \leq 0.001$) higher in RVLM when compared to sham. TNFa was 17.3% ($p \leq 0.001$) greater than sham. In the NTS, IL-6 was 31.4% ($p \leq 0.002$) [N=3 for all groups] greater and TNFa 28.2% ($p \leq 0.0006$) greater pixel density than sham groups. The changes in IL-6 and TNFa cytokine activity may exacerbate the changes in breathing pattern seen during apnea of prematurity or periodic breathing. We do not yet know what mechanism is responsible for changes in breathing during neuro-inflammatory up-regulation but the downstream signaling pathway from these early inflammatory markers is an obvious choice for further investigation.

Disclosures: J. Clay: None. **M. Custer:** None. **R. Johnson:** None. **C.G. Wilson:** None.

Poster

753. Development of Motor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 753.16/A37

Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: 316978

Title: Investigation of the *in vivo* effect of classical and new psychotherapeutic approaches on the behavioural and neurochemical profile of a rat model of Tourette syndrome and control animals - an MRS study

Authors: *F. RIZZO[1], E. NESPOLI[2,5], A. ABEI[3], I. BAR-GAD[6], V. RASCHE[3], B. HENGERER[5], T. BOECKERS[4], A. G. LUDOLPH[2];
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Abstract: Tourette syndrome (TS) is a neurodevelopmental disorder characterized by motor and vocal tics and a high comorbidity-rate with ADHD (attentional deficit/hyperactivity disorder). One third of children with TS experience an improvement of tics during adolescence until young adulthood but a substantial part of patients remains symptomatic after the second decade of life. In both, children and adults, pharmacologic intervention is suggested if tics are distressing and/or interfere with psychosocial function. Different guidelines suggest neuroleptics and alpha-2a agonists as drugs of first-choice. Beside their efficacy on tics, such interventions show severe

side effects. New treatments are required. Aripiprazole, a partial D2 agonist, has been found to be effective in tic-management. Dopamine (DA) metabolism is dysfunctional in TS, but imaging data give definite hints that other neurotransmitters take part in tic generation: histamine, serotonin, norepinephrine, glutamate and GABA, Gutamate and DA metabolism is closely interconnected. The glutamatergic modulator riluzole exerts neuroprotection against glutamate excito-toxicity both *in vitro* and *in vivo*. Clinical trials in TS are ongoing. We compare the effect of neuroleptics (aripiprazole) and glutamatergic drugs (riluzole) on the behavior and cerebral glutamate metabolism during development using MR spectroscopy (MRS) in a TS rat model versus control rats. The recently published model clearly satisfies the face validity criterion in modelling TS. This study will also provide information regarding its predictive validity. WKY rats and spontaneous hypertensive rats (SHR), an ADHD animal model, undergo instrastriatal bicuculline (GABA antagonist) microinjections that induce an acute tic-session. Control animals are sham-operated. MRS spectra are acquired in each group (ARI 1.5mg/kg; RILU 6 mg/kg and vehicle) from PND 35 to 50, covering the evolving period from childhood to young adulthood in rats. Preliminary data on glutamate, GABA, glutamine and lactate absolute quantification in the left dorsal striatum and prefrontal cortex are presented. Preliminary behavioral data of the treated groups - compared to vehicle and sham operated animals - are presented. No differences in the body weight or brain weight in any of the treated groups compared to the vehicle are observed after 15 days of sub-chronic treatment with both drugs. Differences in the MR spectra acquired in rats treated with aripiprazole (classical neuroleptic approach) and riluzole (possible new option) give hints on which cerebral metabolites are influenced by the two different compounds during brain development.

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Poster

753. Development of Motor Systems

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: NIH R01 MH090740

Title: Altered formation and function of striatal circuitry in the absence of Sox8

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Abstract: The striatum is the major component of the basal ganglia and is well known to play a key role in the control of motor function via the indirect (striatopallidal) and direct (striatonigral) output pathways. Imbalances in the activity of these pathways are thought to underlie the behavioral abnormalities observed in a number of neurological disorders including attention deficit hyperactivity disorder (ADHD) and other classical motor disorders. Little is known about the molecular genetic mechanisms that control the formation and function of the direct and indirect pathways. In this respect, we have recently found that the SoxE family member, Sox8, is expressed in the developing and adult striatum. Moreover, we have found that Sox8 marks the direct pathway already at early embryonic stages using Sox8 GFP BAC transgenic mice from GENSAT. By analyzing Sox8lacZ mutant mice, we found that there is a dramatic reduction in the projections of the direct pathway in both homozygous and heterozygous animals, despite the fact that the striatum appears normal in size. To further confirm the specificity of the defect, we crossed Drd1-EGFP (direct pathway marker) BAC mice from GENSAT with the Sox8lacZ mice and our preliminary findings suggest that the EGFP+ fibers terminate prematurely in the globus pallidus (GP, the normal target of the indirect pathway) of homozygous mutants, suggesting that Sox8 is required for long axon growth of direct pathway fibers. In support of this notion, we observed substance P-positive fibers abnormally terminating within the GP of Sox8 mutants. Although basal ganglia circuitry is normally associated with the regulation of motor function, recent studies have suggested roles in social and cognitive behaviors. Because the Sox8 mutants have very specific defects in the formation of the direct pathway, we have conducted several behavioral tests to examine the requirement for normal formation of this pathway in motor, social and cognitive function. Interestingly, Sox8 homozygous and heterozygous mice exhibit increased basal locomotor activity as well as deficits in the social preference assay and the Morris water maze, demonstrating a role for normal striatal circuitry in multiple aspects of brain function.

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Poster

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: 316978

Title: Exploring neurodevelopmental aspects of tics in a juvenile rat model of repetitive behavior

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Abstract: Tourette Syndrome (TS) is a neurodevelopmental disorder which affects 0.4-1% of the population. It is defined by the presence of multiple motor and at least one vocal tic, typically starting during childood. TS is not only about tics. Indeed, up to 90% of all TS patients experience psychiatric comorbidities, mainly ADHD and OCD, but also behavioral disturbances. The exact cause of TS remains elusive, but tics are supposed to be caused by an abnormal regulation of the motor loop activity, which consequentially leads to the hyper-excitability of motor regions of the brain cortex . Dopamine (DA) appears to have a central role, more likely through its fine regulation of the direct and indirect striatal pathways, which in turn regulate voluntary and involuntary movements. Unilateral 6-hydroxidopamine (6-OHDA) lesion in adult rats is a well-established model used in Parkinson´s Disease research. In this model, selective degeneration of nigrostriatal dopaminergic neurons is chemically induced through the administration of 6-OHDA. Subsequent chronic application of dopaminergic agonists challenge leads to the development of repetitive involuntary movements. This is a consequence of striatal increased sensitivity to DA, which is also a putative pathological mechanism of TS, and is induced in this model via previous DA deprivation. The repetitive involuntary movements observed are sudden, rapid and brief, and occur repeatedly at irregular intervals, mainly involving the contralateral forepaw, face and mouth. During the period of levodopa efficacy, the movements change in intensity and frequency, but not in location. Animals can be distracted, and the involuntary movements reduce when they focus on something. The phenotype was challenged using different dopaminergic and non-dopaminergic agents, with a special emphasis on modulators of metabotropic glutamate receptors. Several pharmacological approaches have been shown to interfere with the repetitive movements, either worsening or improving the phenotype, indicating possible lines of therapeutic actions, or co-pathogenic mechanisms. This model could allow the evaluation of the consequences of an altered striatal regulation occurring during development, and could also be employed in the investigation of new therapeutic options for tic disorders.

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Poster

753. Development of Motor Systems

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Program#/Poster#: 753.19/A40

Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Title: Movement learning processes provide potential etiology for neurological disorders

Authors: *J. V. JOSE[1], D. WU[2];
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Abstract: Motor deficits are widely reported in people with social interaction problems suffering from neurological disorders (like Autism Spectrum Disorders (ASD)), suggesting a strong link between motor control and cognitive abilities. In our previous ASD studies, we uncovered small speed fluctuations that break the continuity of speeds versus time profiles via minute speed-Spikes (s-Spikes) at millisecond time scales. Statistical analysis of s-Spikes' results from natural pointing movement trials provided quantitative biomarkers for ASD subjects correlating well with their spoken verbal abilities. Here we ask the general questions: How does the brain maintain or not the continuity of physical movements at millisecond time scales? How does learning a new motor skill modify the smoothness and statistical properties of the speed profiles in subjects with neurological disorders versus typical controls at millisecond time scales? More importantly, how do these motor control mechanisms go awry in neurologic disease? Here we aimed to explore answers to these questions providing information about the possible origins of the s-Spikes. We studied s-Spikes statistics during well-defined movement learning processes, questioning and comparing how and whether or not achieving movement smoothness occurs for both typical controls and subjects with neurological disorders. Our studies aim to shed light on the origins of the s-Spikes statistical differences previously found between typical controls and subjects with neurological disorders, linking movement smoothness to cognitive abilities, and to the potential etiology of the disorders.

Disclosures: J.V. Jose: None. **D. Wu:** None.

Poster

753. Development of Motor Systems

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NSFC (31271148, 31200818, 31260243)

Title: Essential roles of leucine-rich glioma inactivated 1 in the development of embryonic and postnatal cerebellum

Authors: *Y. XIE[1], L. ZHOU[1], J. K. COWELL[2], Y. SHEN[1];
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Abstract: Leucine-rich glioma inactivated 1 (LGI1) is a secreted protein that interacts with ADAM transmembrane proteins, and its mutations are linked to human epilepsy. The function of LGI1 in CNS development remains undefined. Here, we report novel functions of LGI1 in the generation of cerebellar granule precursors (CGPs) and differentiation of radial glial cells (RGCs) in the cerebellum. A reduction in external granule layer thickness and defects in foliation were seen in embryonic and new-born LGI1 knockout (KO) mice. BrdU staining showed an inhibited proliferation of CGPs in KO embryos, which might be explained by the reduced Sonic hedgehog in embryos. In addition, the differentiation of RGCs into Bergmann glias was suppressed in KO mice. Enhanced Jagged1-Notch1 signaling in KO mice via reduced β-secretase proteolysis suggests that altered phenotype of RGCs is due to abnormal Notch1 signaling. Together, our results demonstrate that LGI1 is an essential player in the cerebellar development.

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Poster

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Support: LABEX CORTEX (ANR-11-LABX-0042) of Université de Lyon, within the program“Investissements d'Avenir” (ANR-11-IDEX-0007) operated by the French National Research Agency (ANR)

Title: Massive developmental reduction in the distribution of corticospinal neurons in prenatal macaque

Authors: *A. R. RIBEIRO GOMES[1,2], E. OLIVIER[3], H. P. KILLACKEY[4], C. LAMY[1,2], P. MISERY[1,2], P. GIROUD[1,2], M. BERLAND[5,2], K. KNOBLAUCH[1,2], C. DEHAY[1,2], H. KENNEDY[1,2];
[1]Stem-Cell and Brain Res. Inst., Bron, France; [2]Claude Bernard University, Univ. of Lyon, Lyon, France; [3]Inst. of Neuroscience, Sch. of Medicine, Univ. of Louvain, Brussels, Belgium; [4]Dept. of Neurobio. and Behavior, Univ. of California Irvine, Irvine, CA; [5]Dept. of Obstetrics and Gynecology, Univ. Hosp. Lyon-Sud, Hospices civils de Lyon, Pierre-Bénite, France

Abstract: In the newborn macaque the areal distribution of corticospinal neurons (CSN) is more widespread than that observed in the adult, but overall CSN are mainly found in areas that project in the adult (Galea et al. 1995). Here we have investigated whether the newborn areal distribution of CSN is the consequence of a process of refinement during the 165 days of *in utero* development. The retrograde tracer fast blue was injected at cervical levels of the spinal cord of cynomolgus monkeys at embryonic day (E) 95, E105 and adulthood. At all ages, the soma of the labeled pyramidal CSN were restricted to layer 5; the highest density of labeling was observed in presumptive motor cortex. In the fetal monkeys, the distribution of CSN was considerably more widespread than in the adult with dense projections from regions which do not project in the adult. At E95, CSN form a continuous band spanning prefrontal, frontal, cingulate and parietal cortices. At this developmental stage no CSN were observed in striate cortex and only a few scattered CSN were observed in the inferior temporal region. At E105, the tangential extent of CSN labeling was reduced with respect to the distribution at E95, and neurons were no longer observed in the inferior temporal and prefrontal regions. In the adult, CSN were restricted to motor, somatosensory, cingulate and insular regions, a pattern previously reported in the literature (Galea et al. 1995). Acetylcholinesterase histochemistry allowed to positively identify primary visual (area 17) and auditory cortex. In area 17 there was a complete absence of CSN both at E95 and E105. In contrast, an important number of labeled CSN was observed in primary auditory cortex at both fetal ages. Our results reveal a substantial refinement of the tangential extent of CSN occurring during a restricted developmental time window. This indicates that the restricted areal pattern of CS projections that characterize the postnatal and adult macaque cortex is established subsequently to a sustained and fast elimination of CS projections. The fact that area 17 is free of transient CS projections fits with the absence of transient callosal projecting neurons in this area throughout development (Dehay et al., 1988). In order to gain insight into the developmental mechanisms shaping the CS projections ongoing analysis aims to determine if in the fetus the extensive regions that will show complete loss of corticospinal neurons during later development have significantly lower densities of CSN compared to regions that maintain these connections into adulthood. Support: LABEX CORTEX (ANR-11-LABX-0042) Dehay C, et al. 1988 Nature 331:348-50 Galea MP, Darian-Smith I 1995 Cereb Cortex 5:518-40

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Poster

753. Development of Motor Systems

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Title: Roles of Runx1 transcription factor in axonal projection of mouse embryonic hypoglossal motoneurons

Authors: *M. YOSHIKAWA[1], S. OZAKI[2], M. TOMOYUKI[2], M. MATSUKAWA[1], M. IMADA[1], S. AIZAWA[1], T. SHIGA[2];
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Abstract: Runx1, runt-related transcription factor, plays important roles in the cell type specification and axonal projections of the nociceptive dorsal root ganglion (DRG) neurons. Runx1 is also expressed in the central nervous system as well as the peripheral nervous system, but little is known about the roles in the brain development. In our present study, we found that Runx1 was expressed in the ventrocaudal part of hypoglossal nucleus (nXII) at embryonic day (E) 17.5 and examined the axonal projection and terminal formation of the hypoglossal neurons in the tongue muscles in *Runx1*-deficient mice using antibodies against neurofilament-H and vesicular acetylcholine transporter (VAChT; a presynaptic marker for motor axon terminals). Hypoglossal axon projections to the intrinsic vertical (V) and transverse (T) tongue muscles were sparser in *Runx1*-deficient mice at E17.5 compared with age-matched wild-type mice. Also, the areas immunoreactive for VAChT were reduced in the V and T tongue muscles in *Runx1*-deficient mice. The abnormalities in axonal projection in *Runx1*-deficient mice were not caused by reduction of neurons and abnormality of tongue muscles. We also examined the expression of two markers of cranial motoneurons, c-Met and c-ret. Althouth Runx1 regulates c-Met and c-ret expression in DRG neurons, Runx1 deficiency did not change the expression of these markers in hypoglossal neurons. Thus, it is unlikely that the altered axonal projection from nXII in *Runx1*-deficient mice is associated with c-Met or c-ret dysfunction. Recent studies reported that the Wnt receptor Frizzled3 (Fzd3) also contributes to axonal projection of hypoglossal neurons, so we examined the expression of Fzd3. Fzd3 expression was reduced in the nXII of *Runx1*-deficient mice, suggesting that Runx1 promotes Fzd3 expression. Further studies are necessary to determine whether Fzd3 is involved in the regulation of hypoglossal axonal projection by Runx1. Taken together, our results suggest that Runx1 is involved in targeting ventrocaudal hypoglossal neurons to specific tongue muscles, possibly by interacting with Fzd3.

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Poster

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Title: Retrograde monosynaptic tracing with a recombinant rabies virus reveals transient monosynaptic connections between the corticospinal and motor neurons during development in mice

Authors: ***N. MURABE**[1], S. FUKUDA[1], N. ISOO[1], T. MORI[2], H. MIZUKAMI[3], K. OZAWA[3], Y. YOSHIMURA[2], M. SAKURAI[1];
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Abstract: It is generally believed that direct corticomotoneuronal connections are present only in higher primates, which serve as the basis for their dexterity. Here, we show direct corticomotoneuronal connections in juvenile mice. Retrograde monosynaptic tracing with a recombinant rabies virus from the forearm-innervating motor neurons showed that the corticomotoneuronal cells were widely distributed in the cerebral cortex including the rostral and caudal forelimb area of the motor cortices as well as the primary and secondary somatosensory cortices. Whole cell patch clamp recordings for the forearm-innervating motor neurons detected monosynaptic excitatory postsynaptic current in response to optogenetic stimulation of the corticospinal axons in the spinal cord slices prepared from the postnatal day 8-10 animals. In the fourth postnatal week, however, labeled premotor neurons in the cerebral cortex were not found as far as examined by monosynaptic tracing. Premotor neurons including interneurons in the spinal cord and bulbospinal neurons in the lower brainstem were successfully labeled by monosynaptic tracing. These results suggest that the corticospinal neurons transiently form synapses with forearm-innervating motor neurons in the early postnatal period, which is subsequently eliminated by approximately a month after birth.

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Poster

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Parkinsonfonden

Bertil Hållsten

Kjell & Märta Bejers

Åke Wiberg

Title: Looking at a Vglut2/Pitx2 subpopulation of the subthalamic nucleus - from development to behavior

Authors: *M. PAPATHANOU, N. SCHWEIZER, E. ARVIDSSON, S. PUPE, A. WALLEN-MACKENZIE;
Unit of Functional of Neurobio. - Dept. of Comparative Physiol., Uppsala Univ., Uppsala, Sweden

Abstract: The subthalamic nucleus (STN) is an important area of the basal ganglia known to modulate motor and non-motor aspects of brain functions. Its important role in locomotion has been shown by the successful use of high-frequency stimulation (HFS) of the STN, as treatment for Parkinson's disease, however the mechanisms by which HFS modulate STN activity is unknown. Recently we were able to identify a subpopuplation of the STN, characterized by co-expression of Vglut2 and the paired-like homeodomain2 (Pitx2). Conditional knockout (cKO) of this subpopulation in mice resulted in the manifestation of hyperlocomotion and decreased latency in the initiation of movement. There was decrease of Vglut2 expression and reduction of glutamate transmission. Moreover a closer histological analysis of the cKO mice showed an altered morphology, although it remains unknown whether the changes in morphology and behaviour are attributed to disrupted developmental processes. It is also unclear whether the alteration in the morphology is associated with a loss in a specific subpopulation of the STN. In a

recent screen we were able to identify STN specific markers, which are being analysed in wild-type and cKO mice both at embryonic and young adult stages. Overall our results demonstrate that limiting, but not eliminating, the expression of Vglut2 in the STN is sufficient to achieve results similar to STN high frequency stimulation. However identification of further markers of the STN may improve our basic understanding of this nucleus and may help unravel whether specific subpopulations are responsible for the different core functions of the STN (motor, limbic and associative). This may ultimately provide key insights into the mechanisms underlying deep brain stimulation efficacy and possibly minimize the side-effects that current patients are experiencing.

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Poster

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Title: Neuroanatomical differences between adults who stutter and adults who do not stutter

Authors: *A. DALIRI, E. GOLFINOPOULOS, J. A. TOURVILLE, F. H. GUENTHER; Dept. of Speech, Language, and Hearing Sci., Boston Univ., Boston, MA

Abstract: A growing body of literature suggests that developmental stuttering is associated with neuroanatomical abnormalities, particularly in regions that are involved in speech planning and production (see Bloodstein & Ratner, 2008). Using voxel-based morphometry, several studies have reported abnormalities in both gray matter volume and white matte volume of adults who stutter (AWS) (see Beal et al., 2015). Studies have also reported atypical sulcal morphology in AWS (Cykowski et al., 2008). However, it remains unknown whether AWS who have abnormal grey matter volume also have abnormal white matter volume or atypical sulcal morphology. Therefore, in this study, we examined neuroanatomical differences between AWS and adults who do not stutter (AWNS) using a variety of morphometric measures_cortical thickness, cortical gyrification, grey matter volume, and white matter volume. Moreover, we examined the relationships between different morphometric measures in both AWS and AWNS. Participants were 28 right-handed AWS and 28 right-handed, age- and sex-matched AWNS. The Stuttering Severity Instrument, Fourth Edition (SSI-4) was used to determine stuttering severity of the AWS. Image segmentation, cortical surface reconstruction, surface-based registration, and

surface parcellation were performed using the Freesurfer 5.3 software package. Regional measures of cortical thickness, curvature, gray matter volume, and white matter volume were extracted for specific brain regions of interest (ROI) involved in speech planning and production. In addition, we extracted grey matter volume for subcortical structures. We used general linear models (GLMs) for between-group comparisons. Pearson correlation coefficients were calculated to examine the relationships between different morphometric measures in each group, and between stuttering severity and morphometric measures for the stuttering group. Our preliminary results revealed several morphometric differences between AWS and AWNS. We found increased grey matter volume for AWS in left anterior dorsal premotor cortex, left posterior middle frontal gyrus, and left frontal operculum. We also found increased cortical thickness for AWS in left frontal operculum and right presupplementary motor area. In addition, we found increased cortical curvature for AWS in left posterior middle frontal gyrus, right anterior central operculum, and right parietal operculum. These preliminary results showed that stuttering individuals with atypical grey matter volume are also likely to have atypical cortical curvature and atypical cortical thickness.

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Poster

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HHMI

Title: The COE-type transcription factor UNC-3 cooperates with HOX proteins to generate motor neuron diversity

Authors: *P. KRATSIOS, S. KERK, R. MOURAO, O. HOBERT;
Columbia Univ., New York, NY

Abstract: The motor circuit of *Caenorhabditis elegans* provides an ideal model system to probe the question of how neuronal diversity is generated during development. Similarly to vertebrates, *C.elegans* motor neurons (MNs) are organized into distinct classes that display remarkable functional and anatomical diversity. The underlying basis of such diversity is the differential expression of MN class-specific terminal identity genes (e.g. ion channels, neurotransmitter receptors) that define the specific properties of a functional MN class throughout life. We have previously shown that the evolutionarily conserved COE (Collier, Olf, Ebf) - type transcription factor (TF) UNC-3 is required for diversity in the *C. elegans* ventral nerve cord (VNC) MNs by directly regulating the expression of MN class-specific terminal identity genes. The ability of UNC-3 to activate directly – through its cognate binding site (COE motif) – distinct terminal identity genes in specific MN classes predicts the presence of as yet unknown regulatory factors needed to cooperate with UNC-3 and activate its targets in specific MN classes. Supporting this prediction, transgenic animals carrying a multimerized version of the COE motif fail to show reporter gene expression in any MN class. To reveal the identity of such factors, we followed a candidate approach and found a novel role for HOX genes in MN diversity. Animals lacking gene activity of more anteriorly expressed HOX genes, such as *lin-39*/Scr/Dfd and *mab-5* (Antennapedia-type HOX gene), failed to express terminal identity genes specific to MN classes positioned within the *lin-39* and *mab-5* expression domains. Similarly, the posterior HOX gene *egl-5*/Abd-B is required for expression of terminal identity genes specific to MNs positioned at the posterior end of the VNC. Genetic removal of the HOX cofactor *ceh-20*/Exd/Pbx resulted in similar effects. The presence of HOX/PBX binding sites in proximity to COE motifs in the *cis*-regulatory region of UNC-3 target genes point to a coactivation principle where UNC-3, HOX and PBX factors activate the expression of MN class-specific terminal identity genes, thereby generating MN diversity.

Disclosures: **P. Kratsios:** None. **S. Kerk:** None. **R. Mourao:** None. **O. Hobert:** None.

Poster

753. Development of Motor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 753.27/A48

Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: NIH Grant MH074114 to WEC

NIH Grant AA016662 to RWW

NIH Grant AA013499 to RWW

Title: Dab1 modulates grooming duration in mice

Authors: A. DELPRATO[1,2], B. BONHEUR[1], M.-P. ALGÉO[1], L. LU[3], R. W. WILLIAMS[3], *W. E. CRUSIO[1];
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Abstract: We used the BXD recombinant inbred strains to map quantitative trait loci (QTLs) underlying behaviors associated with open field exploration. Over 900 males and females from 53 strains were observed for 20 min in a rectangular open field (108*49*49 cm). We identified a significant QTL on mouse chromosome 4 influencing grooming duration in both males and females. This narrow interval contains only two genes with different alleles in the C57BL/6 and DBA/2 parental strains: Zcchc11 and Disabled-1 (Dab1). Zcchc11 has no obvious connection to the nervous system or its development. In contrast, Dab1 is a key component of the Reelin signaling pathway that regulates neuronal migration and positioning by activating intracellular signaling cascades and cytoskeletal rearrangement. Dab1scm mutant mice (scrambler) have neuroanatomical abnormalities including degeneration of the cerebellum, hippocampus, and neo-cortex, with concomitant behavioral problems such as ataxia and body tremors. In addition, it has been found that scrambler mice show reduced grooming duration when compared to wild-type controls (Strazielle et al., 2012, Behav Brain Res. 233:24-28). Taken together, this provides strong evidence that the strain difference in grooming duration between C57BL/6 and DBA/2 is, at least in part, caused by allelic variation in the Dab1 gene.

Disclosures: A. Delprato: None. **B. Bonheur:** None. **M. Algéo:** None. **L. Lu:** None. **R.W. Williams:** None. **W.E. Crusio:** None.

Poster

753. Development of Motor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 753.28/A49

Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Title: Role of BDNF and TrkB in the excitatory-inhibitory imbalance during the critical period of postnatal respiratory development in the rat

Authors: H. ZHANG[1], X.-P. GAO[1], *M. T. WONG-RILEY[2];
[1]Cell Biology, Neurobio. and Anat., Med. Col. of Wisconsin, Milwaukee, WI; [2]Med. Col. Wisconsin, Milwaukee, WI

Abstract: Previously, we found that P12-13 is a critical period of respiratory development in the rat, when abrupt neurochemical, metabolic, ventilatory, and physiological changes occur in the respiratory system. During this critical period, there is a distinct imbalance between suppressed excitatory postsynaptic currents (EPSCs) and enhanced inhibitory postsynaptic currents (IPSCs) in respiratory-related hypoglossal motoneurons (HMs). We hypothesized that such an imbalance is contributed by a reduced expression of brain-derived neurotrophic factor (BDNF) and its high-affinity tyrosine kinase B (TrkB) receptors, which normally enhance excitation and suppress inhibition. Indeed, the levels of BDNF and TrkB are significantly down-regulated in multiple respiratory-related brain stem nuclei during the critical period, and the synaptic imbalance was partially reversed by the application of a TrkB agonist (7,8-DHF). To further test our hypothesis, the current study used whole-cell patch-clamp recordings on HMs in brain stem slices of normal rats and those that received i.p. injections of a TrkB antagonist (ANA-12). Results showed that: 1) When ANA-12 was given before the critical period (once a day at P6 and P7, and recordings were done on P8), the amplitude and frequency of sIPSCs were not significantly changed, but the amplitude and frequency of sEPSCs were significantly decreased by 13.03% and 27.89%, respectively. 2) When ANA-12 was given close to the critical period (once a day at P10 and P11 or at P11 and P12, and recordings were done on P12 and P13, respectively), the amplitude and frequency of sIPSCs were significantly increased by 50% and 17.74%, respectively (at P12), and by 20.85% and 16.38%, respectively (at P13). Moreover, the amplitude and frequency of sEPSCs were significantly decreased by 17.32% and 37.3%, respectively (at P12), and by 17.48% and 36.74%, respectively (at P13). 3) When ANA-12 was given after the critical period (once a day at P14 and P15, and recordings were done on P16) , the amplitude and frequency of sIPSCs were also significantly increased by 37.72% and 18.04%, respectively, whereas the amplitude and frequency of sEPSCs were significantly decreased by 19.48% and 28.38%, respectively. Thus, our results indicate that *in vivo* application of ANA-12 significantly aggravates the imbalance during the critical period and exaggerates synaptic inhibition even after the critical period. These findings are consistent with our hypothesis that reduced expressions of BDNF and TrkB directly contributes to the synaptic imbalance within respiratory-related nuclei during the critical period of respiratory development in the rat.

Disclosures: **H. Zhang:** None. **X. Gao:** None. **M.T. Wong-Riley:** None.

Poster

753. Development of Motor Systems

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Topic: A.01. Neurogenesis and Gliogenesis

Support: VICI-ALW Grant 865.09.002 from NWO

Title: Engrailed 1 is required for maintaining proper isthmus positioning

Authors: *W. M. KOUWENHOVEN, J. V. VEENVLIET, L. P. VAN DER HEIDE, J. A. VAN HOOFT, M. P. SMIDT;
Univ. of Amsterdam, Amsterdam, Netherlands

Abstract: Dopaminergic en serotonergic neurons are located in the ventral mesencephalon and rostral metencephalon of the vertebrate brain. Dysfunction in these monoaminergic systems are associated with several severe disorders (e.g. Parkinson's, autism and depression). As such, knowledge on the fundamental and pathological, developmental mechanisms is crucial in the advancement of our understanding of these diseases. For the proper induction of the entire mid- and hindbrain region, Engrailed 1 (En1) homeodomain transcription factor is particularly important. Its expression pattern spans the isthmic organizer (IsO), which is the intracellular signaling center that forms a border between the embryonic midbrain and hindbrain. It is a linear boundary, expressing molecular signals such as fibroblast growth factor family (Fgf)8 and Wnt1. The IsO shapes the development of mesodiencephalic dopaminergic neurons rostral of the IsO and the development of serotonergic neurons caudal of the IsO. Up until now, the investigation into the role of En1 in patterning was hampered due to the perinatal lethality of this mouse model in a Sv/29 background. In the current work we fill that hiatus by investigating the viable, single En1KO embryo and adult animal, using *in situ* histochemistry and electrophysiological recordings. We observed a disrupted IsO in the En1KO animal, leading to the presence of fully functional dopaminergic neurons in the rostral hindbrain, and a simultaneous loss of serotonergic neurons. This establishes the importance of En1 in stabilizing the IsO and in proper patterning of the mid-hindbrain region.

Disclosures: W.M. Kouwenhoven: None. **J.V. Veenvliet:** None. **L.P. Van der Heide:** None. **J.A. Van Hooft:** None. **M.P. Smidt:** None.

Poster

754. Development of Sensory Systems: Vision

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

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Title: Normative development of functional connectivity in the rhesus monkey visual pathways

Authors: *Z. A. KOVACS-BALINT[1], E. FECZKO[1,2,4], B. HOWELL[1,2,4], E. EARL[5], L. LI[3], J. STEELE[1], S. LEE[1], Y. SHI[6], M. STYNER[6], L. PARR[1], J. BACHEVALIER[1], D. FAIR[5], M. SANCHEZ[1,7,4];
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Abstract: Understanding the emergence and developmental trajectories of early social skills and the neural circuits underlying them is critical to unravel the etiology of devastating social disorders such as Autism Spectrum Disorder (ASD), but is still poorly understood, due to limitations of longitudinal, repeated imaging of the infant human brain. Here, we present preliminary findings characterizing the developmental trajectories of social visual engagement neural pathways in a highly translational nonhuman primate (NHP) animal model. Six infant male rhesus monkeys were recruited for this longitudinal resting state functional MRI (rs-fMRI) study. Subjects lived with their mothers in large social groups preserving critical species-specific social experiences. Neuroimaging data were collected at 2, 4, 8, 12, 16, 20 and 24 weeks of age after birth, on a 3T Siemens TrioTim MRI scanner, using an echo planar imaging (EPI) sequence sensitive to BOLD contrast (TR/TE=3sec/30msec, 2x15min, voxel size: 1.5x1.5x1.5mm). Functional connectivity between regions of interest (ROIs) along the visual perception pathway (from V1 to V4 to TEp), the biological motion pathway (from V1 to MT), and their projections to the amygdala (AMY), as well as the spatial attention pathway (from V1 to V3 to LIPv) and its connection to dorsolateral prefrontal cortex (dlPFC, Area 46) were analyzed after top-up distortion correction. Our findings revealed that the primary visual cortex (V1) already shows strong functional connections with other visual cortical areas (V3, V4) at 2 weeks and remains relatively stable with age. Results suggest no age-related changes on the caudal part of the visual pathways, but changes were observed on the rostral part of these pathways from week 2 to 24.

We also found that the AMY-PFC FC becomes stronger during the first 3 months of life, and weaken thereafter. Our results suggest that maturation of the visual pathways in NHPs is likely to continue throughout the first six months of life, in parallel with axon regression and myelination. Increased knowledge on the critical periods of typical development during which early social and visual skills emerge and mature give us opportunity to further understand the neurobiological source of developmental disorders, such as ASD.

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Poster

754. Development of Sensory Systems: Vision

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: NIH1R01EY02391501A1

NIH 1 RO1 EY 02231801A1

Title: Sulcal pits differentially contribute to the development of functional regions in high-level visual cortex

Authors: ***V. S. NATU**, J. GOMEZ, M. A. BARNETT, A. STIGLIANI, K. GRILL-SPECTOR, K. S. WEINER;
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Abstract: The functional architecture of high-level visual cortex is highly consistent relative to cortical folding patterns (Grill-Spector & Weiner 2014). For example, in adults, the parahippocampal place area (CoS-places/PPA) is consistently located in the collateral sulcus (CoS). While the gross anatomical structure and functional topology of high-level visual cortex do not qualitatively change across development, some functional regions quantitatively change, e.g., face- and place-selective regions increase in size and selectivity aross development (Golarai et al., 2007; Scherf et al., 2007). However, it is unknown if quantitative changes of cortical folding occur past age 2 (Meng et al., 2014) and if these developmental changes contribute to the observed structural-functional coupling in adulthood. One quantitative feature of cortical folding is the deepest point in a sulcus, known as the sulcal pit. While sulcal pits have not garnered

attention in research of high-level visual cortex, they are hypothesized to be functionally-relevant (Regis et al., 2005; Im et al., 2010; Auzias et al., 2015; Leroy et al., 2015). We used functional and anatomical MRI in 12 adults (20-40 years old) and 13 children (5-11 years old) to examine (1) if sulcal pits in high-level visual cortex develop, (2) if there is a correspondence between sulcal pits and functional regions, and (3) if such a relationship varies across development. We focused on two regions of the place-selective network - the retrosplenial complex (RSC) and the PPA - because they are both located within primary sulci, the parieto-occipto sulcus (POS) and the collateral sulcus (CoS), respectively. Results reveal that sulcal pits of the CoS and POS develop differentially: the sulcal pit in the CoS is deeper in adults compared to children ($p<0.001$), whereas the sulcal pit of the POS is of similar depth across children and adults ($p=0.64$). Notably, the structural-functional coupling of the sulcal pit and place-selectivity varies across development and anatomical regions. The sulcal pit of the CoS is significantly closer to CoS-places/PPA in adults than in children (mean distance between the pit and the nearest place-selective voxel: adults: MA=0.4±0.2mm, children: MC=5.9±1.7mm, $p < 0.001$), but there was no age difference in the distance between the sulcal pit of the POS and POS-places/RSC (MA=3.9±1.3mm, Mc=4.7±1.2mm, $p=0.62$). These results support a novel hypothesis that the deepening of sulcal pits is an anatomical constraint that may contribute to the functional development of high-level visual cortex where this process occurs along different developmental trajectories depending on the anatomical location.

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Poster

754. Development of Sensory Systems: Vision

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Program#/Poster#: 754.03/A53

Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Title: Transient photoreception in the hindbrain is permissive to hatching in Atlantic halibut

Authors: ***J. HELVIK**[1], O. DRIVENES[2], L. O. E. EBBESSON[3], M. EILERTSEN[1];
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Abstract: Photoreception in animals is often linked to light sensory organs such as the retina to generate images or the pineal to regulate biological rhythms. These structures appear early in development and provide the organism with vital information throughout life. In the past decade

it has become evident that deep brain photoreceptors open for a direct regulation of biological processes within the brain, but few studies have described the existence of light driven pathways. The light-regulated hatching process of Atlantic halibut provides a unique model for studying such direct brain driven processes. In this study we detected a bilateral cluster of photoreceptive cells in the hindbrain of halibut by *in situ* hybridization (ISH). We show that this is a transient cluster that appears just prior to hatching. By a combination of fluorescent ISH and immunohistochemistry we demonstrate that the hindbrain cluster is connected to a neuronal network that projects out into the yolk sac to a narrow band of hatching glands. Our studies with photo-arrested eggs show that dark induced hatching activates the immediate early gene *c-fos* in the hindbrain cluster and in the hatching glands. Strikingly, we show by fluorescent double labelling ISH that the cells of the hindbrain cluster are dual photoreceptive.The cells express both vertebrate ancient opsin and melanopsin that are believed to belong to different classes of photoreceptor pigments normally found in rhabdomeric and ciliary photoreceptor cells, respectively. We here present for the first time in vertebrates that the mRNAs of both photopigments are expressed in the same cells. Taken together our studies show that a transient and dual photoreceptive cell group in the hindbrain mediates hatching in halibut, proposing that transient photoreceptor cells can control specific life history transitions. Further on, the dual photoreceptor cells in a vertebrate can reflect an ancient photoreceptor linage that exists transiently in the hindbrain to control hatching. The concept that an organism can develop transient light sensitivity in specific cell types to target critical aspects of life history transitions provides a new landscape to investigate seasonal timing in animals.

Disclosures: **J. Helvik:** None. **O. Drivenes:** None. **L.O.E. Ebbesson:** None. **M. Eilertsen:** None.

Poster

754. Development of Sensory Systems: Vision

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: NIH EY023871

NIH T32- NS058280

Title: Somatostatin-expressing interneurons in primary visual cortex undergo a developmental switch in neuromodulated excitation

Authors: *C. E. YAEGER, D. L. RINGACH, J. T. TRACHTENBERG;
UCLA, Los Angeles, CA

Abstract: We find that somatostatin-expressing (SOM) interneurons, which inhibit pyramidal (PYR) cell dendrites, receive excitatory neuromodulatory input in early postnatal development that is lost with age. Using resonant scanning two-photon excitation, SOM and PYR cells expressing Gcamp6 were simultaneously imaged in layer 2/3 of the primary visual cortex in critical period-age mice (p28-p30) and adult mice (p40 and older). During imaging, mice were fully awake and able to freely move on a spherical treadmill. Movement and pupil diameter were monitored. Visual stimulation evoked responses in SOM cells at all ages; however, in adult mice SOM cell responses were suppressed during locomotion, whereas in young mice locomotion enhanced evoked responses even in the absence of visual stimulation. Vasoactive intestinal peptide-positive (VIP) interneurons, which innervate and inhibit SOM neurons in adult cortex, do not change activity throughout this developmental time course and do not appear to inhibit SOM cells in young mice. Our data define two large-scale changes in cortical circuit architecture that coincide with the closure of critical period in primary visual cortex: a loss of excitatory neuromodulation to SOM cells and the establishment of VIP-mediated inhibition. Together, these changes shift the effects of locomotion and arousal on SOM cell activity from excitatory during the critical period to inhibitory thereafter. The age-dependent shift in SOM inhibitory activity is expected to profoundly alter dendritic integration and synaptic learning rules.

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Poster

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: NIH Grant P30-GM-32128

Title: Gap junctions shape recurrent activity in the tadpole optic tectum

Authors: Z. LIU[1], C. M. CIARLEGLIO[2], C. D. AIZENMAN[2], *K. G. PRATT[1];
[1]Dept. of Zoology and Physiol., Univ. of Wyoming, Laramie, WY; [2]Neurosci., Brown Univ., Providence, RI

Abstract: The neurons of the Xenopus tadpole optic tectum are organized into layers, with the deepest layer nearest the ventricular surface, and the outer-most layer adjacent to the neuropil. Using a modified horizontal brain slice preparation and focusing on the neurons of the outer layer, we have identified several physiologically distinct populations of neurons. Here we describe one especially distinct population of excitatory neurons that show elevated levels of intrinsic excitability. Similar to well-described deep-layer tectal neurons, these neurons receive relatively strong monosynaptic input from the retinal ganglion cells (RGCs) in the eye, but unlike common deep layer neurons, they receive minimal polysynaptic input - the portion of the RGC-evoked response comprised of recurrent tectal-tectal connections. This suggests that although these neurons receive direct input from RGCs, they receive very little synaptic input from other tectal neurons. Also, by filling these neurons with biocytin, we observed that these neurons display dye-coupling, implying that they could be electrically coupled. Consistent with this, preliminary results indicate that 18beta-glycyrrhetinic acid (18beta-GA), an established gap-junction (GJ) blocker that is known to block electrical coupling in Xenopus tadpole spinal motoneurons, prevents the dye coupling. The unusual pattern of connectivity, elevated intrinsic excitability, and the fact that they are dye coupled, led to the hypothesis that these neurons could synchronize the extensive recurrent portion of the RGC-evoked response received by the common deep layer neurons. To test this we recorded RGC-evoked responses from common deep layer neurons in the presence of 18beta-GA to block the putative electrical coupling. Compared to controls, 18beta-GA significantly reduced the amount of evoked recurrent activity received by deep layer neurons of stage 45-47 tadpoles - the stage when the recurrent portion of the RGC-evoked response is known to be unrefined and longer-lasting. Importantly, 18beta-GA elicited no noticeable effect on the passive electrical properties of individual tectal neurons, ruling out a cell autonomous mechanism, and also did not alter the strength of the monosynaptic portion of the RGC-evoked response. This suggests that gap junctions are a major generator of recurrent activity. A circuit wiring diagram that incorporates these findings places these GJ-coupled outer-layer neurons in a modulatory role that adds a temporal component to the maturing and refining RGC-evoked recurrent activity.

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Poster

754. Development of Sensory Systems: Vision

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: RPB Disney Award to Erik Ullian

Knights Templar Career Starter Award to Tigwa Davis

TMMS Award to Erik Ullian

Title: Visual nucleus-specific targeting and refinement of retinal ganglion cell axons through the cadherin-catenin pathway

Authors: *D. Q. DAO[1], T. H. DAVIS[2], E. M. ULLIAN[1];
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Abstract: Retinal ganglion cells (RGCs) project to central nervous system nuclei, to which they convey visual information from the periphery. Within the image-forming pathway, both ipsilaterally projecting (ipsiRGCs) and contralaterally projecting RGCs innervate relay neurons in the dorsal lateral geniculate nucleus (dLGN), as well as cells of the superior colliculus (SC). In the dLGN, the ipsilateral axons terminate within a territory surrounded by contralateral fibers, while in the SC, the ipsilateral axons pattern themselves ventrally to a larger superficial contralateral territory. The final organization of retinogeniculate (RG) and -collicular (RC) axons requires a highly active process that involves refinement of exuberant axons and synaptic contacts and depends on instructive cues derived from spontaneous retinal activity. Despite a modest yet reasonable understanding of the activity requirements, the molecular events that govern these highly dynamic phenomena remain enigmatic. Due to a trail of evidence that suggests involvement of the cadherin-catenin pathway in activity-mediated synaptic refinement, particularly within visual circuits, we investigated this pathway as a possible mediator of this process. A gene profiling study identified E-Cadherin as a molecule that is modulated by spontaneous activity in the dLGN. Using a Nestin-Cre driver in mice to drive ubiquitous neuronal deletion of floxed genes, we found that while the loss of E-Cadherin does not confer defects in the eye-specific segregation (ESS) of RG axons, the additional loss of p120ctn results in impaired ESS in the dLGN. ESS in the SC was not affected by the double deletion of E-Cadherin and p120ctn, nor was ESS affected in mice with a single p120ctn deletion in either the dLGN or SC. This result is consistent with the hypothesis that redundant cadherin-catenin mechanisms exist in the brain to promote proper circuit development. Using a Cre-driver expressing in ipsiRGCs to exclude presynaptic effects, we demonstrated that the dLGN-specific defect in E-Cadherin/p120ctn null mice likely stems from postsynaptic mechanisms. Furthermore, we showed that another catenin molecule, β-catenin, is an important regulator of both synaptic targeting, as well as refinement in the dLGN. The presynaptic loss of β-catenin results in aberrant multiple ipsilateral dLGN territories as well as ESS defects. Meanwhile, proper ESS is maintained in the SC. Altogether, these data suggest an importance of the cadherin-catenin pathway in targeting and refinement of RG connectivity, while RC circuits,

which are formed from branchings of the same retinofugal axons, are not modulated by this pathway.

Disclosures: **D.Q. Dao:** None. **T.H. Davis:** None. **E.M. Ullian:** None.

Poster

754. Development of Sensory Systems: Vision

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: NIH Grant MH099453

Title: Protocadherins control the modular assembly of neuronal columns in the zebrafish optic tectum

Authors: ***M. R. EMOND**[1], S. COOPER[2], B. LIEBAU[2], M. WOLMAN[3], J. JONTES[2]; [1]Ctr. Molec Neurobiol, [2]Ohio State Univ., Columbus, OH; [3]Univ. Wisconsion, Madison, Madison, WI

Abstract: The assembly of neural architecture during development requires cell-cell recognition to establish and maintain both regional and cellular identities. It is believed that the differential expression of homophilic cell adhesion molecules organizes the patterns of connectivity in developing neural circuits. However, the mechanisms by which cell-cell interactions influence circuit assembly during development are poorly understood. The δ-protocadherins comprise a family of neural adhesion molecules that have been implicated in a range of neurodevelopmental disorders, and mutations in human PCDH19 cause a female-limited form of infant-onset epilepsy. Here we show that the expression of δ-protocadherins partitions the zebrafish optic tectum into radial columns of neurons. Using *in vivo* 2-photon imaging of BAC transgenic zebrafish, we show that pcdh19 is expressed in discrete columns of neurons, and that these columnar modules are derived from proliferative pcdh19+ neuroepithelial precursors. Elimination of pcdh19 results both in a disruption of columnar organization, as well as defects in visually-guided behaviors. Our results demonstrate that the inherited expression of a δ-protocadherin defines neuronal columns and, thus, δ-protocadherins act as molecular tags, both conferring an identity on columns and regulating their development. As we show that other δ-protocadherins define similar columns, this likely represents a fundamental mechanism for organizing the developing nervous system; subdivision of the early neuroepithelium into

precursors with distinct molecular identities would allow the autonomous development of parallel neuronal units, and organize the development of neural circuitry and behavior.

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Poster

754. Development of Sensory Systems: Vision

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: FAPERJ 110.384/2014

Title: The impact of low omega-3/DHA diets on the development of retinofugal projections and differentiation of cholinergic markers in the rat visual system

Authors: ***C. A. SERFATY**[1], P. C. DE VELASCO[2], P. C. SANDRE[1], R. M. DOS SANTOS[3], A. C. F. MELIBEU[4], P. C. C. LOPES[4], B. L. S. A. COSTA[5];
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Abstract: The fine-tuning of visual subcortical connections develop through the selective elimination of misplaced axons and the maintenance of correct axonal branches. In the present work, we studied the impact of a dietary restriction of omega-3 fatty acids on the development of eye specific segregation and topographical specificity of retinofugal pathways. We also studied the impact of low omega-3 diets on the differentiation of retinal layers, cholinergic markers in the developing retina. Female Lister Hooded rats and their litters were fed with either control (soy oil) or restricted (coconut oil) omega-3 diets. At various postnatal ages, rat pups received eye injections of neuronal tracers to visualize retinal axons at their brain targets. Lipid analysis indicated that the experimental diet led to a selective reduction in DHA content in the visual system whereas fish oil supplementation within a specific time window restored DHA levels. Omega-3 restriction induced an increase in the density of retinal axons in the superficial layers of the SC. This effect was observed throughout the stratum griseum superficiale (SGS), including the ventral and intermediate SGS layers at PND13, PND28 and PND42. The same pattern of expanded terminal fields was observed in the retinogeniculate pathways. The supplementation

with fish oil (DHA) for two weeks was able to reverse the abnormal expansion of the retinocollicular projection. Omega-3 restricted groups showed a decrease in RXRα content and CREB phosphorylation (pCREB) in the visual layers of the superior colliculus. Retinal differentiation was also affected by omega-3/DHA deprivation including a reduction in rhodopsin immunolabeling, reduced labeling of cholinergic markers such as VAchT and β2-nicotinic receptors. The data indicate, therefore, that the chronic dietary restriction of omega-3 fatty acids delays axonal elimination and retinal cholinergic differentiation, leading to abnormal development of retinofugal connections. Financial Support: CNPq, FAPERJ, CAPES

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Poster

754. Development of Sensory Systems: Vision

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 754.09/A59

Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: NEI RO1 EY015788

NEI RO1 EY023105

NINDS T32 NS041228

Title: Glutamatergic (stage III) retinal waves and their role in visual development *in vivo*

Authors: *A. GRIBIZIS[1], J. B. ACKMAN[2,1], M. C. CRAIR[1];
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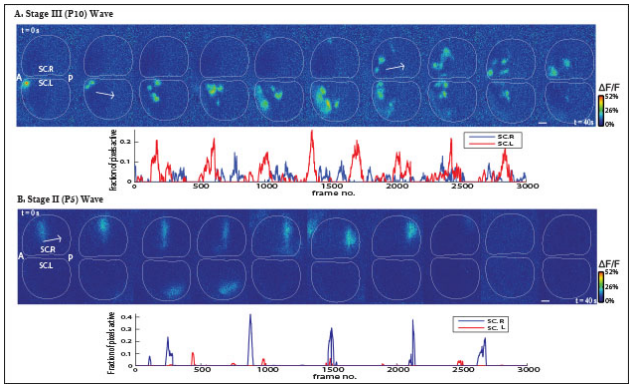
Abstract: In the developing visual system, neighboring retinal ganglion cells (RGCs) fire in correlated bursts of action potentials observed as propagating waves across the retina. These spontaneous waves of activity are thought to be crucial to normal formation of visual system circuitry. Based on *in vitro* experiments in mice, early neonatal ('stage II') waves depend on retinal acetylcholine receptors, while from P10 until around the time of eye opening ('stage III') retinal waves depend on glutamate receptors. Here, we report on our experiments examining the existence and properties of stage III waves in mice *in vivo*. Using optical imaging techniques, we have quantitatively characterized the properties of retinal waves by measuring retinal ganglion cell axon terminal activity in the superior colliculus *in vivo* during the second postnatal week. Our data suggest that stage III retinal waves are more frequent and smaller than stage II waves,

however they still propagate in a wave like fashion, which was not readily apparent from *in vitro* experiments. We have also examined the effects of pharmacological manipulations in the eye on the propagation of retinal waves to the superior colliuclus and higher order visual circuits. These results demonstrate that stage III waves are sensitive to glutamate antagonists *in vivo*, and have unique trans-synaptic propagation compared to earlier (stage II) spontaneous activity, which may be essential in the patterning of circuits throughout the visual system *in vivo*.



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Poster

754. Development of Sensory Systems: Vision

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: NIH Grant NS070022

Title: Critical period for the effect of visual deprivation on the surface area of visual cortex in animals and humans

Authors: ***A. K. ANDELIN**[1], C. KROENKE[2], E. TABER[2], A. STEVENS[2], J. OLAVARRIA[1]; [1]Psychology, Univ. of Washington, Seattle, WA; [2]Dept. of Behavioral Neurosci., Oregon Hlth. and Sci. Univ., Portland, OR

Abstract: Human MRI studies show that blindness has profound effects on the development of the visual system. A limitation of this work is that the subjects are typically grouped into early and late blind even though the age at blindness onset ranges from anophthalmia to blindness starting at 10 or more years of age. Moreover, the early and late categories are not defined with

reference to specific developmental milestones and often do not correspond well across studies. It is therefore difficult to assess the importance that the age at blindness onset has on the nature and variability of anomalies detected with MRI. Mapping out the periods during which visual input is critically needed for the normal development of specific visual structures is important for understanding the role the eyes have during human development. Animal studies have the potential to contribute importantly to this issue because they have demonstrated the existence of different critical periods for several deleterious effects of blindness. Blindness during development induces a reduction in the area size of primary visual cortex (V1) in humans and animals. Using histological and MRI techniques we measured the reduction in the size of V1 induced by bilateral enucleation (BE) at different ages in rats and ferrets, and characterized how the magnitude of the reduction of V1 surface area depends on blindness onset. In sighted and BE rats the size of V1 at maturity was measured from tangential sections of the flattened cortex, while in sighted and BE ferrets the size of V1 at maturity was measured from cortical surfaces derived from post mortem MRI scans. From postnatal day (P) 0 through P12 we observed a graded reduction in the magnitude of the effect of enucleation on the size of V1 in rats. A similar graded response was observed in ferrets enucleated at P7, P20, and P31. Translating the post conceptional timelines of rats and ferrets reveals a quantitatively similar developmental dependence of V1 size on blindness onset in both species. Translating this information to the human post conceptional time line suggests that pathologies inducing blindness at 6 postnatal months or later may have little or no effect on the size of V1. The magnitude of the effect of blindness on the size of V1 is consistent with our MRI measurements from blind subjects affected with retinopathy of prematurity, as well as with MRI data from previous studies. Estimating the critical periods for the deleterious effects of blindness may not only facilitate the interpretation of abnormal MRI data from humans blinded at different ages, but may also help focus therapeutic or restorative efforts on developmental processes that are still plastic at blindness onset.

Disclosures: **A.K. Andelin:** None. **C. Kroenke:** None. **E. Taber:** None. **A. Stevens:** None. **J. Olavarria:** None.

Poster

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: Pervasive and Ambient Computing lab - MVA startup support

Title: Ecologically relevant scoring of binocular receptive field development by innate learning

Authors: I. ADORNO[1], G. KRATZ[2], A. OAKLEY[2], *M. V. ALBERT[2];
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Abstract: In previous computational work, we have shown how spontaneous patterns of neural activity prior to eye-opening can be used as a training pattern for early visual development (so-called "innate learning"). To demonstrate the ecological validity of such a paradigm, we apply a behaviorally relevant scoring approach to evaluate visual codes resulting from various patterns; these patterns are generated in an abstract, but biologically plausible manner. To emphasize the applicability of this principle beyond retinal waves, we have generalized this approach to binocular spontaneous activity, which is known to be present in a wide variety of animals in the LGN and V1 prior to eye opening. Traditionally, success in matching computational to experimental receptive fields focuses on parameter descriptions of derived receptive fields (e.g. spatial frequency) or their response properties (e.g. orientation bandwidth). However, our binocular model provides us with an additional means of scoring the resulting filters, by observing how well the resulting filters can be used to estimate depth. For spontaneous activity generation, we use an abstract, 4-parameter binocular model similar to a percolation network for wave activity but with communication between eye-layers. By varying the cross-talk between layers we vary the correlation between patterns across eye-layers, with an adult-like distribution of disparity selective cells between these extremes. Most importantly, we demonstrate how receptive fields generated from moderately correlated eye layer activity provide the best depth estimation in a stereogram depth estimation task.

Disclosures: I. Adorno: None. **G. Kratz:** None. **A. Oakley:** None. **M.V. Albert:** None.

Poster

754. Development of Sensory Systems: Vision

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: NIH Grant R01 MH086147

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National Science Council, Taiwan Grant 102-2321-B-001-035

Title: Postmitotic regulation of sensory area patterning in the mammalian neocortex by Lhx2

Authors: *A. B. ZEMBRZYCKI[1], C. G. PEREZ-GARCIA[1], C.-F. WANG[2], S.-J. CHOU[2], D. D. M. O'LEARY[1];
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Abstract: The mammalian neocortex is divided into specialized modality-specific areas that are responsible for the processing of sensory information. This architecture is critical, because altered area size affects normal sensory function and behavior in animals and humans. Current knowledge suggests that cortical sensory area identity is controlled by transcription factors (TFs) that specify area features in progenitor cells and subsequently their progeny in a one-step process. However, how neurons acquire and maintain these features is unclear. We have used conditional inactivation restricted to postmitotic cortical neurons in mice to investigate the role of the TF LIM-homeobox 2 (Lhx2) in this process and report that in conditional mutant cortices area patterning is normal in progenitors but strongly affected in cortical plate (CP) neurons. We show that Lhx2 controls neocortical area patterning by regulating downstream genetic and epigenetic regulators that drive the acquisition of molecular properties in CP neurons. Our results question a strict hierarchy in which progenitors dominate area identity, suggesting a novel and more comprehensive two-step model of area patterning that incorporates these revelations and define the relevance of postmitotic mechanisms in determining the functional properties of cortical areas: In progenitors, ‘patterning TFs’ prespecify sensory area blueprints. Sequentially, sustained function of ‘alignment TFs’, including Lhx2, is essential to maintain and to translate the blueprints into functional sensory area properties in cortical neurons postmitotically. In summary, our findings add novel insights into the sequence and hierarchy of mechanisms that regulate the layout of the cortex into sensory areas postmitotically and reemphasize critical roles for Lhx2 that acts as one of the terminal selector genes in controlling principal properties of neurons. The revised model has major implications for the understanding and for the further investigation of the complex neurodevelopmental mechanisms that establish proper sensory circuits and their functions.

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Poster

755. Development of Limbic, Olfactory, and Gustatory Systems

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: 5P50MH090966-05

Title: 5HTTLPR modulates transient non-canonical SERT expression and connectivity in the developing macaque brain

Authors: *M. K. CAFFREY CAGLIOSTRO[1], R. BANSAL[3], S. GERUM[4], K. WALSH[2], N. SEPULVEDA[2], A. ZIOLKOWSKI[1], V. ARANGO[2], D. GUILFOYLE[4], J. A. GINGRICH[1], M. S. ANSORGE[1];
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Abstract: Alteration of serotonin (5-HT) signaling during development is believed to influence risk for certain psychiatric disorders. One way in which 5-HT signaling is modulated is through expression of the serotonin transporter (SERT), which sequesters extracellular 5-HT. Although in adulthood SERT is produced by classic 5-HTergic neurons of the raphe nuclei, during development rodents display a transient, non-canonical expression of SERT throughout sensory and limbic systems. This non-canonical SERT expression is essential for proper sensory system development in mice, and is proposed to modulate limbic system development as well. Here we investigated if non-canonical SERT expression is evolutionarily conserved and studied SERT expression in the developing macaque (macaca mulatta) brain. Because the macaque genome harbors a homologue of the human 5HTTLPR, a polymorphism in the promotor region of the gene encoding SERT, we also studied if SERT expression is affected by its allelic composition. To investigate if the 5HTTLPR broadly affects brain development, we also performed diffusion tensor imaging (DTI). We find a robust and widespread expression of SERT throughout limbic and cortical regions during GD100, which decreases across development. We furthermore find reduced SERT expression in limbic regions of s allele carriers. Lastly, we detected a robust effect of the 5HTTLPR on GD100 and PN40 DTI measures, with reduced connectivity in individuals carrying two “s” alleles compared to individuals carrying at least one “l” allele. Taken together our data suggest that the 5HTTLPR influences structural aspects of brain development through altering non-canonical developmental SERT expression, which might impact risk for adult psychopathology.

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Poster

755. Development of Limbic, Olfactory, and Gustatory Systems

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

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Title: Social rank and diet affect amygdala functional connectivity with prefrontal cortex during infancy in female Rhesus Macaques

Authors: *M. PINCUS[1], J. GODFREY[1], E. FECZKO[1], E. EARL[2], Y. SHI[3], M. STYNER[3], L. LI[1], B. HOWELL[4], D. FAIR[2], K. ETHUN[5], M. WILSON[1], M. SANCHEZ[1];
[1]Emory Univ., Atlanta, GA; [2]Oregon Hlth. & Sci. Univ., Portland, OR; [3]Univ. of North Carolina, Chapel Hill, NC; [4]Inst. of Child Development, Univ. of Minnesota, Minneapolis, MN; [5]Emory University, Yerkes Natl. Primate Res. Ctr., Atlanta, GA

Abstract: Connectivity between the prefrontal cortex (PFC) and amygdala (AMYG) is critical for emotional and stress regulation, and alterations in this circuitry are implicated in anxiety and mood disorders. Because the maturation of these neural circuits is protracted during childhood, the development of PFC-AMYG connectivity may be particularly susceptible to social stress. Recent research demonstrates that obesity may also compromise the development of these circuits, which is associated with greater incidence of anxiety and mood disorders. Given that stress is a risk factor for obesity in children, the presence of both conditions could synergistically impair the development of emotion regulation circuits. Because disentangling the effects of social stress versus diet on brain development is difficult in human studies, the aim of this study was to use a naturalistic model of psychosocial stress (social subordination) with or without access to a calorically dense diet (CDD) to examine the impact of each of these factors on the neurodevelopment of PFC-AMYG functional connectivity. Thus far, subjects are 14 socially-housed infant female rhesus macaques, whose mothers are either dominant (DOM, n=7) or subordinate (SUB, n=7). Within each rank category, a subset of subjects and their mothers had access to a low-calorie diet (LCD) only, and the other had access to both a CDD and LCD (CHOICE), resulting in four rank-diet groups (n = 2 DOM+CHOICE, n = 5 DOM+LCD, n = 4 SUB+CHOICE, n = 3 SUB+LCD). As infant rhesus monkeys actively nurse but begin to wean at ~ 2 mo of age, resting-state functional MRI scans (2 x 15 mins) were obtained at 6 mo of age to

examine effects of rank and diet on the development of PFC-AMYG functional connectivity (FC). FC was extracted and analyzed with a region of interest (ROI)-based analysis, using medial PFC (Brodmann areas (BA) 24, 10, 32), orbitofrontal cortex (OFC; BA 11, 13), and AMYG as the a priori ROIs. Preliminary analysis of the data with our current sample suggests that SUB monkeys had decreased FC between OFC (BA 13) and AMYG relative to DOM monkeys. Intake of a CDD diet during infancy was associated with increased FC between the OFC (BA 13) and AMYG across all subjects. SUB monkeys in the CHOICE condition had higher connectivity between mPFC (BA 10) and AMYG, relative to SUB monkeys fed only the LCD. Because OFC-AMYG circuitry plays a role in reversal learning and goal-directed behavior, our data suggests that consumption of CDD and social stress may affect these behaviors by altering this circuitry in infant female macaques. Further analysis will assess whether the observed PFC-AMYG FC differences are related to feeding behavior and emotion regulation.

Disclosures: **M. Pincus:** None. **J. Godfrey:** None. **E. Feczko:** None. **E. Earl:** None. **Y. Shi:** None. **M. Styner:** None. **L. Li:** None. **B. Howell:** None. **D. Fair:** None. **K. Ethun:** None. **M. Wilson:** None. **M. Sanchez:** None.

Poster

755. Development of Limbic, Olfactory, and Gustatory Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 755.03/A65

Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Title: Epigenomic dissection of sexually dimorphic neural circuits

Authors: *R. BRONSTEIN, M. V. WU, J. TOLLKUHN;
Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: Our lab is interested in understanding the molecular and epigenomic events governing sex differences in the brain and behavior. Neural circuit nodes controlling sex-specific behaviors are shaped by the gonadal hormones estrogen and testosterone. Male critical periods of CNS sexual differentiation occur just after birth, and are reliant upon the conversion of circulating testosterone to estrogen in the brain, in an aromatase-dependent manner. Females represent the default neural circuit template, only during puberty does estrogen begin to shape the sexual maturation of their brains. In adulthood both males and females require their cognate hormonal streams to finely tune and maintain a rich array of sex-specific social behaviors. Following gonadectomy, although these behaviors are heavily diminished - the underlying neural circuits persist and behavior can be restored following exogenous treatment with hormones. However,

the genes and regulatory mechanisms utilized by these hormones to activate behavioral circuitry are not known. Two key brain regions that integrate olfactory information from conspecifics to mediate the display of sex-specific behaviors are the bed nucleus of the stria terminalis (BNST) and the medial amygdala (MeA). We use genetic strategies to perform ChIP-seq and RNA-seq specifically in Cre-defined populations of neurons from these brain regions in males and females at distinct developmental time points. Ultimately our goal is to identify novel cis-regulatory DNA elements (promoters, enhancers etc.), as well as trans-acting chromatin modulators, which in unison function to underpin diverse sex-specific behavioral repertoires.

Disclosures: **R. Bronstein:** None. **M.V. Wu:** None. **J. Tollkuhn:** None.

Poster

755. Development of Limbic, Olfactory, and Gustatory Systems

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: NIH Grant MH105759

NARSAD Independent Investigator Grant

Title: Roles of thalamocortical interactions in the development of mouse prefrontal cortex

Authors: A. PROUE, *Y. NAKAGAWA;
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Abstract: The thalamus and the neocortex establish reciprocal connections during early development. Recent studies discovered that interactions between these two brain regions are crucial not only for adult brain functions, but also for the development of the neocortex. This has been best demonstrated in primary sensory areas, where area-specific thalamocortical projections play a role in establishing characteristic patterns of gene expression in these areas and the neuronal fate appropriate for the source of the incoming thalamocortical afferents. However, it is unknown whether the thalamus plays a similar role in the development of other neocortical areas. The prefrontal cortex (PFC) is a center for higher cognitive functions and emotions, and defects of its development are implicated in many developmental brain disorders including schizophrenia and autism. In this study, we sought to determine if thalamocortical interactions are required for proper PFC development. In previous studies, we showed that the mice that lack the homeobox gene Gbx2 in a thalamus-specific manner have defects in thalamocortical

projections and that characteristic expression patterns of genes including RORβ, Cdh8 and Lmo4 in primary sensory areas are altered at early postnatal stages so that these areas no longer exhibit clear boundaries with the surrounding higher-order sensory areas. Interestingly, however, expression of these molecular markers appeared unchanged in the PFC in thalamus-specific Gbx2 mutant mice. This result prompted us to identify several genes that are preferentially expressed in the developing PFC. We found that one of these genes, Cyp26b1, which encodes an enzyme that degrades retinoic acid, was specifically reduced in layer 6 of the medial and ventral PFC at postnatal day 8, but unaltered in other parts of the rostral and medial neocortex as well as in the hippocampus. In contrast, mice that ectopically express tetanus toxin light chain in a thalamus-specific manner showed no obvious reduction of Cyp26b1 expression in the PFC, whereas in primary sensory areas, these mice showed defects in gene expression similar to those found in Gbx2 mutant mice. These results suggest that the developing PFC requires interactions with the thalamus that are fundamentally different from those used for the development of the sensory neocortex. Our results also implicate that the thalamus may control retinoid signaling in the PFC by regulating the expression of Cyp26b1.

Disclosures: **A. Proue:** None. **Y. Nakagawa:** None.

Poster

755. Development of Limbic, Olfactory, and Gustatory Systems

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Title: PAX6 haploinsufficiency association with reduced amygdala volumes

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Abstract: The *PAX6* gene is known to play a critical role in eye and brain development. It acts as a transcription factor ensuring successful neurogenesis and occulogenesis. *PAX6+/-* patients have characteristic aniridia due to inadequate regulatory activity during the formation of the lens and retina. Mutation of this gene in mice also affects the migration and differentiation of cells involved in the morphogenesis of the amygdaloid complex. The present study investigated possible associations between heterozygous *PAX6* mutation and amygdala volumes as measured by morphometric analysis of MRI brain scans. Twenty-three healthy controls (HV) and twelve *PAX6+/-* patients with heterozygous point mutations or intragenic deletions within *PAX6*

underwent MRI brain scans. Mean ages for the HV and *PAX6+/-* groups were 21.2 (SD 12.3) and 28.9 (SD 13.4), respectively. MRI brain scans were obtained using a Philips Achieva 3 Tesla scanner paired with an 8-channel head coil. T1-weighted whole brain volumes consisting of one hundred and seventy 1-millimeter thick sagittal slices with an in-plane resolution of .9375 by .9375 were collected using a 3D T1-TFE pulse sequence (TR=4.85 msec.; TE=2.17 msec.; flip angle= 15 degrees). Amygdala volumes were generated by processing the brain images through FreeSurfer (version 5.3) subcortical segmentation. Although the groups did not significantly differ with respect to age, age as well as sex were entered as covariates in the analysis. Right and left amygdala volumes were summed together to form a total amygdala volume measure. ANOVA with age and sex as covariates revealed a highly significant difference between the two groups ($F = 14.76$, $p < .001$). The *PAX6* group had a mean total amygdala volume of 3173 cubic millimeters compared to the larger HV group mean of 3684 cubic millimeters. Both age ($F = 0.50$, $p = .825$) and sex ($F = 2.56$, $p = .119$) covariates were not significant. These results support previous findings from animal studies demonstrating the critical role of *PAX6* in the development of specific nuclei in the amygdaloid complex (Tole, Remedios, Saha, & Stoykova, 2005). Tole, S., Remedios, R., Saha, B., & Stoykova, A. (2005). Selective requirement of Pax6, but not Emx2, in the specification and development of several nuclei of the amygdaloid complex. *J Neurosci*, 25(10), 2753-2760.

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Poster

755. Development of Limbic, Olfactory, and Gustatory Systems

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Title: Early maternal care modulates the development of emotional neurocircuitry in nonhuman primates: amygdala functional connectivity

Authors: *E. L. MORIN[1,2], B. HOWELL[4], K. REDING[5], D. GUZMAN[2], E. FECZKO[2], E. EARL[6], Y. SHI[7], M. STYNER[7], D. FAIR[6], M. SANCHEZ[3,2];
[2]Yerkes Natl. Primate Res. Ctr., [3]Dept. of Psychiatry & Behavioral Sci., [1]Emory Univ., Atlanta, GA; [4]Insititute of Child Develop., Univ. of Minnesota, Minneapolis, MN; [5]Natl. Inst. of Mental Hlth., Bethesda, MD; [6]Dept. Of Behavioral Neurosci., Oregon Hlth. & Sci. Univ., Portland, OR; [7]Dept. of Psychiatry, Univ. of North Carolina, Chapel Hill, NC

Abstract: Maternal care is vital in primates for proper socioemotional and cognitive development. Maltreatment during infancy is associated with increased risk for psychopathology, and social and cognitive deficits. This is perhaps due to alterations in cortico-limbic circuits (i.e. prefrontal cortex (PFC) and amygdala connectivity) critical for emotional and stress regulation, which are sensitive to early experience and stress due to their protracted development. How these effects unfold during early development is not well understood and difficult to study in humans. This study utilized a well-established nonhuman primate model of maternal maltreatment (MALT), which consists of comorbid physical abuse and rejection, leading to infant distress. In macaques, the highest rates of abuse in the first three months of life co-occur with rapid brain development and maturation of PFC-amygdala circuits. MALT leads to long-term effects on emotional reactivity and social behavior, as well as alterations in white matter development. To disentangle the effects of experience from those of inheritance we used a unique cross-fostering experimental design with random assignment of half of the rhesus monkey infants to control or maltreating foster mothers at birth. This study further delves into the effects of MALT on the developmental trajectory of PFC-amygdala functional connectivity (FC) throughout infancy. Structural MRI and resting state fMRI scans were collected at postnatal ages 2 weeks and 3, 6, 12, and 18 months in 13 MALT (7 males, 6 females) and 13 control infants (6 males, 7 females). Correlated activity between these regions was found to have strong hemispheric differences, both developmentally (left hemisphere FC stronger, more positive, than right) and between experimental groups (MALT had weaker, less positive, FC than controls). In control animals, amygdala FC with medial PFC (mPFC) and dorsolateral PFC (dlPFC) became less positive with age, reaching close to zero or negative correlations by 18mos, while the connectivity with orbitofrontal cortex (oPFC) became more positively correlated. Amygdala-PFC FC was less positively correlated in both hemispheres of MALT animals in comparison with controls, and showed increasingly negative correlation throughout development in the right hemisphere, especially in mPFC and dlPFC. The oPFC, however, showed stronger positive FC through development in MALT than controls. These findings suggest alterations in functional coupling of amygdala-PFC regions (i.e. reduced FC) during infancy and the early juvenile period in MALT subjects, which could influence their emotional, cognitive, and behavioral development.

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Poster

755. Development of Limbic, Olfactory, and Gustatory Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 755.07/A69

Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Title: A role for the zinc finger transcription factor Tshz1 in the migration and differentiation of the intercalated cells (ITCs) of the amygdala

Authors: *J. KUERBITZ[1], S. EHRMAN[1], A. N. GARRATT[3], R. R. WACLAW[2], K. CAMPBELL[1];
[1]Developmental Biol., [2]Cancer Biol. and Neural Tumors, Cincinnati Children's Hosp., Cincinnati, OH; [3]Inst. of Cell Biol. and Neurobio., Charite Universitatsmedizin Berlin, Berlin, Germany

Abstract: The intercalated cell (ITC) groups of the amygdala are clusters of GABAergic interneurons that surround the basolateral complex of the amygdala and have been shown to modulate amygdalar control of anxiety responses. Previous studies have demonstrated that ITCs originate in the embryonic dorsal lateral ganglionic eminence (dLGE) at embryonic time points. The zinc finger transcription factor Tshz1 is expressed in a subpopulation of cells in the embryonic dLGE and in mature ITCs. However, the importance of *Tshz1* expression for ITC development remains unknown. We have utilized germline *Tshz1*^{GFP} knock-in/knock-out mice to follow the normal development of ITCs and to investigate whether *Tshz1* expression is necessary for proper development of ITCs. E18.5 *Tshz1* knockout mice (*Tshz1*$^{GFP/RA}$) show an ectopic cluster of GFP positive cells at the dorsal, medial border of the Lateral Amygdala (LA) and a severe reduction of ITC cells on the lateral side of the basolateral complex and in the main intercalated nucleus. These findings suggest that ITCs can be generated in the absence of Tshz1 but their migration and settling patterns in the amygdala are dependent on its function. Furthermore, many of the clumped ITCs in the mutant amygdala ectopically express the dLGE transcription factors Sp8 and Pax6 suggesting that Tshz1 plays a role in the down-regulateion of these factors as they migrate toward the amygdala. Additionally, the remaining, but misplaced, Tshz1^{GFP} expressing cells show reductions in the ITC markers FoxP2 and Meis2, suggesting an impaired ability to develop into mature ITCs. Postnatal mice harboring *Dlx1-cre* mediated, basal

forebrain specific loss of *Tshz1* show continued mislocation of amygdalar GFP expressing cells, which show nearly complete loss of FoxP2 expression as well as ectopic expression of the striatal projection neuron marker FoxP1. Our data suggest that *Tshz1* may play an important role in regulating migration and gene expression in developing ITCs. We are currently performing gene-expression analysis on migrating ITC progenitors in *Tshz1* mutants to identify additional genes functioning downstream of *Tshz1* during ITC development. Future studies will determine the effect of the ITC phenotype in Tshz1 mutants, on fear and anxiety behaviors.

Disclosures: J. Kuerbitz: None. **S. Ehrman:** None. **A.N. Garratt:** None. **R.R. Waclaw:** None. **K. Campbell:** None.

Poster

755. Development of Limbic, Olfactory, and Gustatory Systems

Location: Hall A

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Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: JSPS KAKENHI Grant Number 25430042

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Grants-in-aid for Scientific Research in a Priority Area from the Ministry of Education, Science, Sports, and Culture 17082006

Title: Collapsin response mediator protein 4 (CRMP4) knockout mice showed physiological alterations related to olfactory function

Authors: *A. TSUTIYA[1], M. NISHIHARA[3], Y. GOSHIMA[4], R. OHTANI-KANEKO[1,2]; [1]Grad. Sch. of Life Sci., Toyo Univ., Gunnma, Japan; [2]Bio-Nano Electronics Res. Ctr., Toyo Univ., Saitama, Japan; [3]The Univ. of Tokyo, Tokyo, Japan; [4]Yokohama City Univ., Kanagawa, Japan

Abstract: Members of the collapsin response mediator protein (CRMP) family (CRMP1-5) were reported to be involved in the pathogenesis of various neuronal disorders including schizophrenia and autism spectrum disorder (ASD). One of them, CRMP4, is reported to participate in aspects of neuronal development such as axonal guidance. However, no physiological or behavioral phenotypes in Crmp4 knockout (Crmp4-KO) mice have been identified, making it difficult to elucidate the *in vivo* roles of CRMP4. We previously found strong expression of Crmp4 mRNA in the olfactory bulb (OB) during the early postnatal period, suggesting crucial roles for CRMP4

in OB development. In this study, we aimed to test whether Crmp4-KO pups would exhibit abnormal olfaction. In addition, we tried to reveal the possible mechanisms underlying any impaired olfactory ability found. In order to investigate olfactory ability, we assessed ultrasonic vocalizations (UVs) emitted by wild-type (WT) and Crmp4-KO pups, which are one of the easily detectable olfaction-dependent behaviors in pups. We revealed that Crmp4-KO pups at postnatal day 7 (PD7) had impaired olfactory ability for discriminating between familiar and unfamiliar nest-bedding odors. Next, we compared the physiological features of the OB between WT and Crmp4-KO pups by studying the expression of c-Fos, an activity-dependent neuronal marker, in the OB after olfactory stimulation of ethyl acetate (EA), a commonly used non-biological odorant. We found that the EA-elicited c-Fos expression in the OB at PD7 is much greater in Crmp4-KO pups than in WTs, indicating abnormal activity of the OB neurons in Crmp4-KO pups. In addition, the mRNA and protein expression levels of glutamate receptor 1 (GluR1) and GluR2 were exaggerated in Crmp4-KO pups relative to other excitatory and inhibitory receptors and transporters, raising the possibility that enhanced expression of these excitatory receptors contributes to the hyperactivity phenotype and impairs olfactory ability. This study provides an important animal model for elucidating the roles of CRMP4 in the development of higher brain functions. GluR1 and GluR2 have been implicated in many nervous system disorders associated with development, including ASD. It has also been suggested that increased activity in excitatory neurons gives rise to the social and cognitive deficits observed in ASD. In addition, impaired olfaction has been reported in ASD. Therefore, we hypothesized that Crmp4-KO mice exhibit behavioral abnormalities relevant to ASD. To test the hypothesis, we next performed several animal behavioral tests including social interaction test.

Disclosures: **A. Tsutiya:** None. **M. Nishihara:** None. **Y. Goshima:** None. **R. Ohtani-Kaneko:** None.

Poster

755. Development of Limbic, Olfactory, and Gustatory Systems

Location: Hall A

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Program#/Poster#: 755.09/A71

Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: NIH Grant R01 NS085568

VA National Merit Award

Title: Long-term effect of neonatal isoflurane exposure on the olfactory system in rats

Authors: *J. LEE[1,3], J. ZHANG[1], Z. WEI[1,3], L. WEI[1,2], S. YU[1,3];
[1]Dept. of Anesthesiol., [2]Neurol., Emory Univ., Atlanta, GA; [3]Ctr. for Visual and Neurocognitive Rehabil., Atlanta VA Med. Ctr., Decatur, GA

Abstract: Isoflurane is a volatile anesthetic agent widely used in infants and neonates. Emerging data from preclinical and clinical studies have shown that anesthetic exposure of neonates may cause neuronal degeneration in the developing brain, leading to functional deficits such as learning and memory disabilities later in juvenile and adulthood. However, the effect of neonatal exposure to isoflurane on olfactory cells and olfactory function is obscure. In the present study, we investigated the effect of isoflurane exposure on olfactory system in neonatal rats. Wistar rat pups were exposed to 1.5% isoflurane for 3 hr at postnatal day (P) 3, P4, and P5, respectively. At the juvenile age of P26-27, buried food finding test showed that animals previously exposed to isoflurane took significantly longer times to locate buried food compared with normal animals. Consistently, impaired odor distinguishing function was seen in juvenile rats that were exposure to isoflurane. The expression of olfactory marker protein (OMP) normally found in mature olfactory sensory neurons was significantly reduced in the olfactory bulb and epithelium in juvenile rats with neonatal isoflurane exposure. In addition, TUNEL staining revealed an increase of neuronal degeneration in the granule cell layer (GCL) and glomerular layer (GL) of rats with neonatal isoflurane exposure compared to normal animals. Increase of activated caspase-3, caspase-8, and caspase-9 were observed in the olfactory bulb in juvenile rats with neonatal isoflurane compared with normal animals, indicating increased apoptotic cell death. Furthermore, these cell deaths in the olfactory bulb were accompanied by the selective death of the GABAergic neurons. Lastly, to examine the effect of neonatal isoflurane exposure on neurogenesis, 5-bromo-2-deoxyuridine (BrdU) was administered to all animals once daily until sacrifice. In juvenile rats with neonatal isoflurane exposure, there was a significant decrease in the number of NeuN+/BrdU+ cells compared with the normal animals, indicating reduced neurogenesis. Taken together, our initial findings suggest that neonatal isoflurane exposure causes not only increased olfactory neuronal degeneration but also reduced neurogenesis, probably leading to olfactory functional deficit in juvenile rats.

Disclosures: **J. Lee:** None. **J. Zhang:** None. **Z. Wei:** None. **L. Wei:** None. **S. Yu:** None.

Poster

755. Development of Limbic, Olfactory, and Gustatory Systems

Location: Hall A

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Program#/Poster#: 755.10/A72

Topic: A.06. Development of Motor, Sensory, and Limbic Systems

Support: NIH Grant DC007176

Title: Expression of the TrkB receptor declines before birth dividing taste neurons into two equal subpopulations

Authors: *J. RIOS-PILIER, R. F. KRIMM;
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Abstract: Taste neurons (which carry chemical information from taste buds of the tongue to the brain) could be a single subpopulation of similar neurons whose function is dictated solely by which receptor cells they innervate. Alternatively, taste neurons could differentiate into subtypes during development defined by differences in expression and function. Embryonically, brain-derived neurotrophic factor (BDNF) regulates the development of most taste neurons, but postnatally, BDNF becomes restricted to subpopulations of taste receptors cells with specific functions. We speculated that the primary receptor for BDNF, TrkB, may also become developmentally restricted to a specific neuronal subtype. To test this possibility, we used a combination of genetic labels, one that identifies taste neurons (Phox2b-Cre::tdtomato) and one for TrkB (TrkB-GFP) to quantify TrkB receptor expression in taste neurons. We found only half of the Phox2b-positive taste neurons (399 vs 203) were TrkB-positive in whole-mount geniculate ganglia. Since at E11, all geniculate ganglion neurons express TrkB, BDNF must be developmentally down-regulated. To determine when this occurs, we quantified the TrkB receptor in taste neurons at E13.5, E15.5, E17.5, P0, P20 and P60 (adult). Most taste neurons expressed TrkB during embryonic stages (E13.5=96%, E15.5=91%, E17.5=90%). By P0, only 58%±7 of taste neurons still expressed TrkB, which was similar to adults (52%±1). Thus, TrkB is down-regulated during late embryonic development. Many non-taste neurons (P2X3-positive, Phox2b-negative) of the geniculate ganglion also expressed TrkB, but did not down-regulate TrkB to the same extent as taste neurons. These findings indicate that there is a specific decline in TrkB expression during development of taste neurons just before birth. Since neurotrophin signaling can regulate neuronal differentiation, it is possible that differential TrkB-signaling regulates the differentiation of a subpopulation of taste neurons with specific functions. Since not all gustatory neurons are embryonically TrkB-dependent, it is possible that neurons which down-regulate TrkB during development also survive in its absence, we are currently testing this idea with a combination of genetic labels and conditional TrkB knockouts. These findings suggest that taste neurons are not a homogenous population but can be divided into separate subpopulations based on TrkB-expression and dependence; future studies will determine how differences in taste neuron differentiation are reflected in taste function.

Disclosures: J. Rios-Pilier: None. **R.F. Krimm:** None.

Poster

756. Evolution of Development

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 756.01/A73

Topic: A.08. Evolution of Developmental Mechanisms

Support: T32 GM007183

Title: Next-gen sequencing and an evolution-based search for neocortical layer 4 genes

Authors: *S. D. BRISCOE[1], C. B. ALBERTIN[1], J. J. ROWELL[1], C. W. RAGSDALE[2];
[2]Dept. of Neurobio., [1]Univ. of Chicago, Chicago, IL

Abstract: The long-distance axon projections of mammalian neocortical layer 5 (L5) cells allowed for the identification of novel marker genes through retrograde tracing and cell sorting. A parallel search for layer 4 (L4) markers has been hindered by the absence of such projections. We took advantage of connectional and molecular studies that demonstrate neocortical L4 homologs are present in specific nuclei in the avian dorsal telencephalon. The avian brain offers important advantages over the neocortex for the identification of novel marker genes: 1) the large size of avian L4-like nuclei allows for their dissection with minimal contamination by unwanted cell types and 2) marker genes conserved across mammals and birds are likely to be functionally important. We carried out Illumina sequencing on E14 chicken brain tissue isolated from two L4-like nuclei (entopallium and field L), one L5-like nucleus (arcopallium), and one control nucleus of unknown homology (mesopallium). Reads were assembled with Trinity and abundance estimations were calculated using RSEM. Progressive filtering of the transcripts based on pairwise comparisons of expression levels produced a list of transcripts enriched in the L4-like nuclei. We selected the most highly expressed protein-coding genes from this list as candidate genes to be validated by *in situ* hybridization on E14 chicken telencephalon. Of the 21 genes tested to date, 19 are highly enriched in L4-like nuclei. This approach also recovered *cEAG2,* a previously known selective marker gene for neocortical L4 and avian L4-like nuclei. These data will be extended to other taxa to identify genes with conserved expression. Our findings indicate that next generation sequencing provides reliable quantitative data on gene expression and is an effective tool for the identification of avian nuclear marker genes.

Disclosures: S.D. Briscoe: None. **C.B. Albertin:** None. **J.J. Rowell:** None. **C.W. Ragsdale:** None.

Poster

756. Evolution of Development

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 756.02/A74

Topic: A.08. Evolution of Developmental Mechanisms

Support: Commission of Shanghai Municipality 14411962000

Title: Visual cortex activation in early monocular and binocular blind macaque: a BOLD-fMRI study during auditory tasks

Authors: *Z. TANG, L. WU;
Eye & ENT Hosp. of Fudan Univ., Shanghai, China

Abstract: Objective: To study adaptive plasticity and reorganization in the visual cortex of the early monocular or binocular blind macaque using task-based blood oxygenation level dependent function MRI (BOLD-fMRI). Methods: Six healthy neonatal macaques were randomly divided into three groups. One group served as control group (group A). Optic nerve transecting was performed in the right eye of another group to establish the monocular blind model (group B), and also the same operation was performed in the binocular optic nerve of the last group for establishing the binocular blind model (group C). Sixteen months after the operation, BOLD-fMRI was used for examining visual cortex activation of each macaque (in group A, B and C) during auditory stimulation of pure tone and bird sounds, respectively. All of BOLD response changes in both visual cortex and auditory cortex of all three groups were further compared with the immunofluorescent staining findings, respectively. Results: During two kind of auditory tasks, greater BOLD activity was noted in the visual cortex of macaque in group B and group C compared with group A, while BOLD responses were higher in the left visual cortex than in the right one of same macaque in group B. Whereas, compared with group A, lower BOLD activity was found in the auditory cortex of group B and group C during the same auditory stimulations. All of these findings can be further confirmed by the immunofluorescent staining using c-fos antibody. Additionally, parietal lobe and frontal lobe BOLD activity were also observed in the group B and group C. Conclusions: Both monocular and binocular blindness macaque can recruit visual cortex to carry out the auditory tasks after their visual deprivation, which indicated the establishment of cross-modal plasticity within visual and auditory cortex.

Disclosures: **Z. Tang:** None. **L. wu:** None.

Poster

756. Evolution of Development

Location: Hall A

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Program#/Poster#: 756.03/A75

Topic: A.08. Evolution of Developmental Mechanisms

Title: BRWD1 associated chromatin regulatory mechanisms in Trisomy 21

Authors: *L. FARRELLY[1], A. LEPACK[1], Y. LU[1], W. WENDERSKI[4], A. SOSHNEV[4], R. CAO[5], H. LI[5], R. ROPER[6], K. BRENNAND[2], T. W. MUIR[7], I. MAZE[1,3];
[1]Pharmacol. and systems therapeutics, [2]Dept. of Psychiatry, [3]Dept. of Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY; [4]Lab. of Chromatin Biol. and Epigenetics, The Rockefeller Univ., new york, NY; [5]Ctr. for Structural Biology, Dept. of Basic Med. Sciences, Sch. of Med., Tsinghua Univ., Beijing, China; [6]Dept. of Biol., Indiana University, Purdue Univ., Indianapolis, IN; [7]Dept. of Chem., Princeton Univ., Princeton, NJ

Abstract: Down syndrome (DS) is the most common chromosomal abnormality disorder in humans caused by a triplication of all or part of chromosome 21. DS is associated with physical growth delays, characteristic craniofacial abnormalities and intellectual disability. Although much is known regarding physiological aberrations associated with DS, far less is known about the molecular mechanisms mediating the disease. Although DS is clearly marked by deficits in neural plasticity and increased neurodegeneration, few treatments exist that adequately reverse neuronal impairments and/or cognitive deficits. Given that several neurological disorders associated with cognitive impairment (e.g., DS, ATRX syndrome, Rett syndrome, etc.) result in disruptions in gene regulation, in part, via epigenetic processes, further mechanistic studies of neuronal specific histone function promise to provide clues into the underlying causes of neurodevelopmental pathology. Here, we identify chromatin-associated BRWD1 as a neuronally enriched 'reader' protein putatively involved in DS associated neurological deficits. BRWD1 is a WD40 repeat and bromodomain-containing protein that is encoded within the Down syndrome critical region 2 on chromosome 21 in humans, and to date, very little is known regarding its function. Since WD40 propeller domains have previously been shown to interact with histone methylation signatures, we sought to identify whether it might act as a multivalent binding protein that can recognize and simultaneously associate with multiple distinct histone posttranslational modifications, many of which (e.g., H3K4me1, H3K27me3 and H4K20me3) we have found to be significantly altered in human DS neurons (iPSC derived) and in forebrain tissues from a mouse model of DS (Ts65Dn mice with segmental trisomy 16, which are at a dosage imbalance for genes corresponding to human chromosome 21q21-22.3, including BRWD1, and exhibit mild to moderate learning and behavioral deficits). Recombinant human BRWD1 WD40 and bromodomains were purified, and custom histone PTM peptide arrays, as well as individual peptide IPs, have confirmed high affinity and specific interactions with these marks *in vitro*. Using a combination of classic chromatin biochemistry, chemical/structural biology and functional neuroscience approaches, we are investigating the consequences of BRWD1 triplication in DS in relation to altered patterns of gene expression in affected

individuals, with the hope that such information may aid in the development of improved therapeutics aimed at alleviating DS associated pathologies.

Disclosures: **L. Farrelly:** None. **A. lepack:** None. **Y. Lu:** None. **W. Wenderski:** None. **A. Soshnev:** None. **R. Cao:** None. **H. Li:** None. **R. Roper:** None. **K. Brennand:** None. **T.W. Muir:** None. **I. Maze:** None.

Poster

756. Evolution of Development

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 756.04/A76

Topic: A.08. Evolution of Developmental Mechanisms

Title: Patterns and gradients of neurogenesis in the avian dorsal thalamus

Authors: *L. L. BRUCE, A. M. LYNN, D. A. SCHNEIDER;
Biomed. Sci., Creighton Univ., Omaha, NE

Abstract: The dorsal thalamus relays sensory and motor information between areas of the brainstem and the telencephalon. Although all vertebrates have a dorsal thalamus, which is believed to be derived from a common ancestral anlage, the extent to which the various nuclei are comparable in birds and mammals has been strongly debated. One approach to addressing this question is to compare the thalamic gradients and patterns of neurogenesis. To characterize these in the avian dorsal thalamus, a single application of a low dose of bromodeoxyuridine (BrdU) was delivered to each chick between embryonic day (E)3 and 8 (stage 21 and stage 34), followed by survival to E10 (stage 36). Comparisons of anti-BrdU labeling patterns across the different injection days suggest that nearly all dorsal thalamic neurons are born early in chick embryogenesis, between E3 and 8. Furthermore, neurons in the lateral, dorsal, and posterior parts of the dorsal thalamus are generally born earlier than those in the medial, ventral, and anterior parts. Analyses of the birthdates for nine thalamic regions show that the general pattern of neurogenesis in the avian dorsal thalamus resembles that of homologous regions within the rodent thalamus, with the exception of the auditory region, nucleus ovoidalis, which is born earlier than the mammalian auditory medial geniculate nucleus. Neuronal production begins at a similar time throughout the thalamus, but is completed earlier in the posterior thalamus. The nucleus tractus septomesencephalici and lateral geniculate are formed earliest wave of neurogenesis, followed by rotundus, and then the dorsal group. Nucleus ovoidalis and the medial thalamic group are formed in the last wave. The similar pattern of neurogenesis in birds and mammals may represent a highly conserved developmental pattern that was present in the

common ancestor of living birds and mammals, or may represent independently derived states. Additional studies in reptiles and amphibians are needed to distinguish between these evolutionary histories.

Disclosures: L.L. Bruce: None. **A.M. Lynn:** None. **D.A. Schneider:** None.

Poster

756. Evolution of Development

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 756.05/A77

Topic: A.08. Evolution of Developmental Mechanisms

Title: DSCAM promotes cell death

Authors: *S.-F. YOU[1], S.-K. CHEN[2];
[2]Life Sci., [1]Natl. Taiwan Univ., Taipei, Taiwan

Abstract: Each type of neuron except photoreceptor rods and cones in the retina forms "Retinal mosaics" that cover whole retina with an even spatial distribution. This pattern assures every horizontal cell, amacrine cell and retinal ganglion cell well-arranged within their layer, covering entire retina without blind spot with minimum dendritic field overlapping. However, the mechanism behind the phenomenon remains unknown. Recent researches find apoptosis may involve in the formation of retina regularity. The constant numbers of retina neurons rely on steady proliferation and apoptosis. Mice with the pro-apoptotic gene *bax knockout* or overexpress of the anti-apoptotic gene *bcl-2* showed disrupted spatial pattern. Intriguingly, the same phenotype has been reported in the *dscam* (Down's syndrome Cell Adhesion Molecules) knocked out mice. Furthermore, the dendrites of neighboring cell severely tangle together. Therefore, we hypothesize that DSCAM is involved in the retina apoptotic pathway by homophilic interaction between the same cell types which lead to apoptosis-depended retina mosaic formation. Using *in vitro* experimental setup, we found that overexpressing of DSCAM could promote cell death. This research could provide a further detail of the formation retinal mosaic.Key word: Retina tiling, Retina mosaics, eye development

Disclosures: S. You: None. **S. Chen:** None.

Poster

756. Evolution of Development

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Program#/Poster#: 756.06/A78

Topic: A.08. Evolution of Developmental Mechanisms

Support: Acadmia Sinica Grant AS-104-TP-B09-2

Title: Regulation of interneuron distribution by the fate of cortical projection neurons

Authors: Z.-X. NIOU, *S.-J. CHOU;
Academia Sinica, Taipei, Taiwan

Abstract: Mammalian cerebral cortex is comprised of distinct cortical regions, for example six-layered neocortex that processes vision, audition and somatosensation, and three-layered paleocortex, including piriform cortex (PC) that processes olfaction. Neocortex and PC both arise predominantly from dorsal telencephalic (dTel) progenitors of an Emx1 lineage that express Lhx2, a LIM homeodomain transcription factor in a graded, position-dependent level. We showed previously that Lhx2 controls a binary fate decision of dTel progenitors to generate neocortex versus PC. When Lhx2 is deleted by Emx1-Cre in the dorsal telencephalon in the Lhx2 conditional knockout (cKO), the lateral neocortex is refated to form an ectopic piriform cortex. Inhibitory cortical interneurons (INs), which use γ-amino butyric acid (GABA) as their main neurotransmitter, are primarily generated in the medial ganglionic eminence (MGE) of ventral telencephalon (vTel) and enter the cortex by tangential migration. The migration of INs from the MGE to cortex is controlled by a complex combination of long-range and short-range attractant and repelling signals. The mechanisms regulating the migration of INs to their final destination are not fully understood. Using a panel of IN makers, we investigate the distribution of INs in Lhx2 cKO cortex. We observed changes in IN distribution in the cKO cortex when compared with wild type littermates. This suggests that the fate of cortical projection neurons plays a role in regulating IN distribution.

Disclosures: Z. Niou: None. **S. Chou:** None.

Poster

756. Evolution of Development

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Topic: A.08. Evolution of Developmental Mechanisms

Support: James S. McDonnell Foundation grant 220020293

Title: Variation in neuron numbers across the marsupial and primate isocortex: evidence of shared and derived characters across mammals

Authors: *C. J. CHARVET[1], C. D. STIMPSON[1], M. A. RAGHANTI[2], A. H. LEWANDOWSKI[3], F. M. KRIENEN[1], C. C. SHERWOOD[1];
[1]Ctr. for the Advanced Study of Human Paleobiology, The George Washington Univ., Washington, DC; [2]Kent State Univ., Ohio, OH; [3]Cleveland Metropolis Zoo, Cleveland, OH

Abstract: It is generally assumed that marsupial mammals exhibit few cortical neurons under a unit of cortical surface area, yet relatively few marsupials have been examined and little is known about cross-cortical variation in neuron numbers in this diverse clade. We used the optical disector method to investigate the number of neurons per unit of cortical surface area across several marsupial mammals (i.e., red kangaroo, parma wallaby, koala). We compared these findings to those previously obtained for primates with other mammals. In contrast to the notion that the marsupial isocortex has fewer neurons compared with eutherian mammals, we found that neurons per unit of cortical surface area in marsupial mammals overlap with those found in eutherian mammals (e.g., rodent, cat). Similar to what has been observed in eutherian mammals, most of the variation in neuron numbers across the width of the cortex of marsupial mammals is accounted for by upper layer (layer II-IV) neurons. Furthermore, the cortex of marsupial mammals is characterized by more neurons in the caudo-medial pole of the lateral cortex and the primary somatosensory cortex than in lateral and medial regions. This is in contrast with primates where neurons per unit of cortical surface area increase from the rostral to the caudo-medial pole. A comparison of previous reports examining neurogenesis timing in marsupial, rodents and primate species suggests that, with the exception of the primary somatosensory cortex, evolutionary changes in neuron numbers across the adult cortex coincide with evolutionary changes in the pattern of neurogenesis timing in development. Taken together, these findings highlight that evolutionary changes in the spatial pattern in developmental duration account for evolutionary changes across the cortex of mammals.

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Poster

756. Evolution of Development

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Program#/Poster#: 756.08/A80

Topic: A.08. Evolution of Developmental Mechanisms

Support: University Grants commision

Title: Activation of Non-LTR retrotransposons specific transcripts in rats in response to stress

Authors: *S. MUKHERJEE, JR[1], D. SHARMA[2], K. C. UPADHYAYA[1];
[2]Scool of Life Sci., [1]Scool of Life Sciences, Jawaharlal Nehru Universit, New Delhi, India

Abstract: Objectives Basic objectives were to analyze the transcriptional regulation of L1Rn elements in response to stresses. Methods Real time PCR analysis using RNA isolated from various brain regions and various tissues from old and young wistar rats was carried out to determine the change in L1 transcripts. Results There was no significant change in the expression of L1Rn in various brain regions of 2 month old and 18 month old rats except cerebral cortex. The heavy metals nickel, cadmium, lead, mercury and aluminum upregulates the expression of L1 in tissue specific and age dependent manner. Conclusions The results of this investigation conclusively prove that LINE1 retroelements are transcriptionally activated in response to stress.

Disclosures: S. Mukherjee: None. **D. Sharma:** None. **K.C. Upadhyaya:** None.

Poster

756. Evolution of Development

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Topic: A.08. Evolution of Developmental Mechanisms

Support: NSF-IOS#1122180 to LBD

Title: Do the Sexiest Dancers Have the Largest Little Brain?: Associations between display complexity and both brain volume and cerebellar granular layer volume in manakins(Pipridea)

Authors: *G. PANO[1], W. R. LINDSAY[2], L. B. DAY[1];
[1]Biol., The Univ. of Mississippi, Oxford, MS; [2]The Univ. of Gothenburg, Gothenburg, Sweden

Abstract: Lekking male manakins (Pipridae) attract mates using non-vocal acrobatic displays that require precise motor control with complexity varying widely across species. These displays often involve high-speed flight, production of mechanical sounds, and cooperative dance among

males. There is sexual dimorphism of the brain in at least one manakin species with complex display, Manacus vittellinus. In this species, a visuomotor integration area is larger in females that fly to specific perch sites to track the fast moving display of males, and females are known to select mates on the basis of 10s of milliseconds differences in performance of a display element. Males have larger arcopaliums and marginally significant larger cerebellae, sensorimotor and motor coordination brain regions, respectively. Previous studies have shown that bowerbirds, (oscines that build complex display sites "bowers"), have a positive association between bower complexity and both brain and cerebellum volume. To determine whether we would find similar results in the suboscine manakin, which performs practiced acrobatic displays (rather than learned bower building) we measured brain volume and attributes of cerebellar (CB, "the little brain") morphology in 12 manakin species and a closely related fly-catcher. We have previously shown that brain weight is positively associated with manakin display complexity. Brain volume is highly correlated with brain weight ($r=0.87$, $p<.0001$) and can provide generalizations and replication of our previous findings. Brain volume adjusted for bird weight was positively related to display complexity ($R2=.30$, $p<0.05$), supporting the positive association found between brain weight and complexity. As no significant phylogenetic signal between brain weight and display complexity was detected in our previous study and brain weight and brain volume are highly correlated, it is unlikely that phylogenetic corrections are needed for the brain volume/complexity associations. Measurements of CB granular layer and CB molecular layer volumes show a marginally positive association between the granular layer volume and display complexity ($R2=0.267$, $p=0.071$), but no association between the molecular layer volume and complexity. Correction for phylogenetic non-independence of samples is incomplete and may change this result. Our data confirm that sexual selection can act on motoric displays resulting in coevolution of larger brains, and possibly larger "little brain" cells for motor planning and coordination.

Disclosures: G. Pano: None. **W.R. Lindsay:** None. **L.B. Day:** None.

Poster

756. Evolution of Development

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 756.10/A82

Topic: A.08. Evolution of Developmental Mechanisms

Title: Cortical gyrification induced by a hominoid-specific gene HSG1 in the mouse brain

Authors: ***X. JU**[1], Q.-Q. HOU[1], A.-L. SHENG[1], K.-Y. WU[1], T. WEN[2], Z. YANG[3], X. WANG[4], Z.-G. LUO[1];
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Abstract: It is generally assumed that the expansion of the mammalian neocortex during evolution correlates with the increase in intelligence. To fit into a limited cranium, expanded cortical surfaces are folded to form gyri and sulci. The molecular mechanisms underlying the expansion of the cortex remain poorly understood. Recent cross-species studies have shown the emergence of an outer subventricular zone (OSVZ) in the primate cortex, consisting of a massive pool of proliferating basal progenitors (BPs), which are rare in lissencephalic murine cortex. The radial and lateral expansion of BPs is thought to be the cause of cortical folding of gyrencephalic species, although direct experimental evidence is still lacking. Here, we report that a hominoid-specific gene HSG1 promotes generation of BPs and induces gyrus-like structures when expressed in the mouse cortex. Expression of HSG1 in cortical progenitors in the ventricular zone of the mouse embryo via in-utero electroporation disrupted adherens junctions and caused delamination of ventricular radial glia by down-regulating the expression of N-cadherin. Immunostaining of mitotic markers and real-time imaging showed that HSG1-expressing delaminated basal cells underwent self-renewal and exhibited the morphology of typical outer (basal) radial glia, the most abundant type of BPs in primates. Furthermore, we observed extensive cortical folding and gyrus formation in transgenic mice expressing HSG1 as well as in mice electroporated with HSG1 in cortical progenitors. Thus, we have identified a duplicated gene in humans that regulates the expansion and folding of the cortex and delineated the molecular and cellular mechanisms underlying its action.

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Poster

756. Evolution of Development

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Topic: A.08. Evolution of Developmental Mechanisms

Support: Research support funds from the Queensland Brain Institute

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National Health and Medical Research Council (NHMRC) C.J. Martin Fellowship (P.K.)

Title: Development of neocortical interhemispheric connections in a pre-callosal marsupial

Authors: *R. SUAREZ[1], A. PAOLINO[1], L. MORCOM[1], P. KOZULIN[1], L. R. FENLON[1], L. J. RICHARDS[1,2];
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Abstract: The most remarkable evolutionary innovation in the brain of placental mammals was the rewiring of interhemispheric connections through the corpus callosum. This provided a shorter route for integration of bilateral circuits, significantly increasing the speed of information processing. We found that marsupials share an ancestral template of commissural wiring with monotremes, despite being more closely related to placentals. Therefore, here we studied the development of these connections in a marsupial model, the fat-tailed dunnart, to elucidate what events could have triggered callosal evolution. By EdU birth-dating and *in vitro* retrograde labeling, we find that olfacto-recipient structures pioneer commissural formation. Then, deep-layer neocortical neurons send axons that are followed by upper-layer axons, as revealed by sequential in-pouch electroporation of reporter genes. Deep-layer axons wait at the subplate to innervate the cortical plate at the same time as upper-layer axons. An interesting finding is the co-existence of independent neuronal populations with laterally- and medially-oriented axonal projections, suggesting the existence of a proto-callosal phenotype in the common ancestors of marsupials and placentals. We discuss these findings in terms of general developmental processes directing commissure formation in mammals and possible developmental scenarios explaining evolution of the corpus callosum.

Disclosures: R. Suarez: None. **A. Paolino:** None. **L. Morcom:** None. **P. Kozulin:** None. **L.R. Fenlon:** None. **L.J. Richards:** None.

Poster

756. Evolution of Development

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Topic: A.08. Evolution of Developmental Mechanisms

Support: NRF grant (NRF-2013R1A1A2009209)

Hyundai NGV

Title: Detection of drowsiness in driving simulation using EEG and fNIRS

Authors: ***S. AHN**[1], T. NGUYEN[2], H. JANG[1], J. KIM[1,2], S. JUN[1];
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Abstract: Drowsiness is the main cause of car accidents compared to other factors such as over-speed or inattention. Generally, it is hard to shake off drowsiness and we are going to drowsy state regardless of our intention. Therefore, we need to predict driver's drowsiness and detect the symptom of drowsy state before falling sleep to reduce the car accidents. In this study, we investigated the drowsiness in terms of brain signal by performing virtual driving simulation using simultaneous EEG and fNIRS recording. Subject took a virtual driving simulator designed by Hyundai Motor Company and drove about 20 minutes. To make subject drowsy, subject did not sleep whole night and participate in experiment in the morning. Sixty-four EEG channels were attached on entire scalp and custom-built 12 channels fNIRS system was used hemodynamic changes on forehead in 0.5 seconds sampling interval. We adopted modified Beer-Lambert law and converted intensity of light into concentration changes. In EEG analysis, we applied independent component analysis to remove artifacts generated by moving and calculated the relative power level (RPL) which powers of specific frequencies divided by total power of 1-50Hz range. In this study, theta (4-7Hz) and alpha (8-13Hz) RPLs were calculated because drowsiness is most related to these frequency bands. In figure 1(a) depicted hemodynamic changes corresponding to oxy/de-oxy/total hemoglobin changes on 2 channels among 12 channels. Yellow and green-colored regions indicate awake and drowsy state, respectively. These states are accord with manually inspection by experimenters. Oxyhemoglobin concentration changes (HbO) gradually increase in drowsy state and return to base line in awake state and deoxyhemoglobin concentration changes (HbR) reamain in baseline. Total hemoglobin (THb) is simple summation of these two values. Figure 1(b) described the theta and alpha RPL corresponding to each state of fNIRS results. Theta RPL in drowsy state increases around central region compared to awake state and alpha RPL has lower values on whole regions in drowsy state.

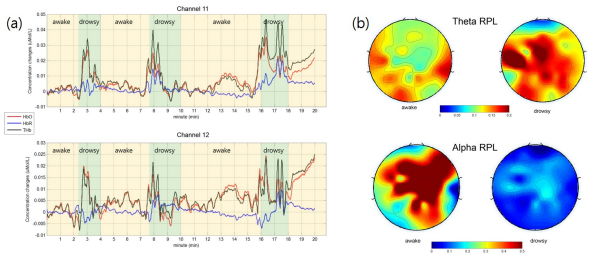

Figure 1. (a) : Concentration changes of fNIRS data. Yellow and green-colored indicate the awake and drowsy state, respectively.
(b) : Theta and alpha RPLs of EEG data. Each topography means relative power in awake and drowsy state.

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Poster

757. GPCR II

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Program#/Poster#: 757.01/A85

Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant NS047198 (AKD)

NIH Grant NS070715 (DES)

Title: Influence of aromatic moieties linked to piperazine ring of tetrahydrobenzo[d]thiazole based hybrid compounds impacts efficacy of dopamine D2/D3 agonists at D3 receptors

Authors: ***M. E. REITH**[1,2], J. ZHEN[1], T. ANTONIO[1], J. C. JACOB[3], D. GRANDY[4], A. K. DUTTA[5], D. E. SELLEY[3];
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Abstract: The work described here addressed the question as to whether small structural differences in agonists at D_2 and D_3 dopamine receptors can affect their intrinsic efficacy. We compared two compounds developed in our earlier work (Ghosh et al., 2010; Biswas et al., 2008): D-264 and D-301. Both contain the tetrahydrobenzo[d]thiazole moiety, connected through a (propyl)N-ethyl linker with a piperazine biphenyl moiety (D-264) or a piperazine isoquinolin moiety (D-301). The first series of experiments involved WT mice in which both D_2 and D_3 receptors contribute to G protein activation, and D_2 KO mice in which the D_2 component has been removed. Both agonists produced similar maximal stimulation of [^{35}S]GTPγS binding in caudate-putamen (CPu) (52-53%) and nucleus accumbens (NAcc) (30-34%) of WT mice. In D_2 KO mice, however, the D-301 E_{max} value was significantly greater than that of D-264 (17% versus 5%, respectively) in CPu. In NAcc, only D-301 significantly stimulated [^{35}S]GTPγS binding in D_2 KO mice (E_{max} ~ 10%), whereas D-264 did not stimulate [^{35}S]GTPγS binding above basal levels. These results suggest that D-301 activates D_3 receptors more efficaciously than D-264. In the second series of experiments, D-264 and D-301 appeared to act in the [^{35}S]GTPγS assay as full agonists at D_2 and D_3 receptors expressed in CHO-cells; it is well known that partial agonists can display full agonist behavior at receptors overexpressed in cell

systems. By comparing K_i values from [^{35}S]GTPγS assays with EC_{50} values from [^{3}H]spiperone binding assays under identical conditions, we were able to determine intrinsic activity which is determined in part by K_i/EC_{50}, i.e. receptor reserve (Selley et al., 1998). D-301, but not D-264, showed a K_i/EC_{50} ratio statistically greater than unity (similarly to DA itself) in D_3 but not in D_2 receptor-expressing cells. Because $G\alpha_o$ is highly expressed in the brain and is important in D_3 G protein coupling, $G\alpha_o$ was transiently co-expressed in CHO cells. At D_3 $G\alpha_o$ led to an intrinsic efficacy significantly higher than unity for D-301 but not D-264; DA itself had a higher than unity intrinsic activity both in the absence and presence of $G\alpha_o$. D-301 had a 64% greater intrinsic activity than D-264 in D_3 $G\alpha_o$ cells; no such difference was seen in D_2 $G\alpha_o$ cells. The results from the two series of experiments combined indicate that D-301 has a greater intrinsic efficacy at D_3 than D-264, whereas the two compounds act on D_2 with similar intrinsic efficacy. This D_3 intrinsic efficacy difference manifests as different E_{max} values for G-protein activation in striatum of D_2 KO mice, where D_3 receptor density is low and $G\alpha_o$ expression is high relative to transfected CHO cells.

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Poster

757. GPCR II

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Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant R15NS078645

BYU Mentoring Environment Grants

Title: The putative cannabinoid receptor GPR55: expression, modulation of hippocampal plasticity and behavior

Authors: *K. M. HURST, C. BADGLEY, M. YOUNG, Z. COWAN, J. CALL, J. WELCH, T. ELLSWORTH, J. EDWARDS;
BYU, Provo, UT

Abstract: Learning and memory occur due experience-dependent changes in our brain in response to our environment. These changes are mediated by synaptic plasticity, particularly within the hippocampus. Plasticity can either strengthen or weaken synapses, known as long-

term potentiation (LTP) or long-term depression (LTD) respectively. While many forms of plasticity are NMDA-dependent, endocannabinoids mediate several new forms of hippocampal synaptic plasticity. Endocannabinoids bind to receptors such as cannabinoid receptor 1 (CB1) and transient receptor potential vanilloid 1 (TRPV1) in various brain areas including the hippocampus. However, research has demonstrated a non-CB1/TRPV1-dependent endocannabinoid synaptic plasticity in the hippocampus. While the receptor(s) involved is currently unknown, several potential candidate receptors that bind the endocannabinoid anandamide have been identified. These are among the orphan G-protein coupled receptors (GPRs) whose distribution in the brain and/or function is not well known. GPR55 is of particular interest as it activates second messenger systems, including IP3-mediated increases in intracellular calcium. Using quantitative RT-PCR, electrophysiological and memory behavioral tasks we examined hippocampal GPR55 expression and function. GPR55 is expressed in hippocampus of both rats and mice. Interestingly, application of the GPR55 agonist LPI (2 μM) to wild-type mice demonstrates a significant enhancement of LTP in brain slices. This LPI effect was absent in GPR55 knock-out (KO) mice, which exhibit significantly ($p < 0.05$) smaller LTP (146%) than wild-type (WT) (181%). The GPR55 antagonist, CID 16020046, (10 μM) also blocked LPI enhancements in WT mice. While examining CA1 LTD preliminary data illustrate no significant difference to this point between KO and WT mice. GPR55 also appears to increase release probability (Sylantyev et al., PNAS, 2013), denoting a presynaptic role. Therefore, we examined paired-pulse ratios (PPR) between KO and WT mice in the presence and absence of LPI. Indeed, while there is only a slight difference between KO and WT PPRs, after application of LPI there is a significant increase in PPR of WT mice not noted in KO mice. Behaviorally, KO and WT mice did not differ in the novel object recognition test, but we are now investigating spatial navigation, using radial arm maze to examine spatial memory. These data suggest GPR55 is expressed and physiologically relevant in the hippocampus. Because enhanced LTP is usually associated with better memory performance in rodents, this provides a potential target to enhance the cellular mechanism associated with memory formation.

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Poster

757. GPCR II

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Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant R01ES03299

MSU College of Veterinary Medicine

Title: Elevation of intracellular Ca^{2+}mediated by methylmercury toxicity was delayed by dopamine receptor antagonists in pheochromocytoma cells (PC12)

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Abstract: Perturbation of synaptic transmission is a pathophysiologic mechanism by which methylmercury (MeHg) - induced toxicity occurs. In the brain, the dopamine (DA) system appears to be affected by MeHg as exhibited by 1) increased of DA release, 2) inhibited DA uptake, 3) altered DA synthesis and metabolism and 4) reduced type II dopamine receptor D2R expression. Still, no study has tested for direct effects of MeHg on DA receptor functions. This study aimed to examine effects of acute exposure to MeHg on D1R and D2R regulation of [Ca2+]i. The D1R antagonist SCH23390 or D2R antagonist raclopride were applied to differentiated PC12 cells for 30 min before MeHg administration. Real time [Ca2+]i changes were analyzed using Fura2-AM microfluorimetry. Normally in PC12 cells, MeHg application causes a multiphasic increase in fura-2 fluorescence; at least two kinetically-distinct phases occur. Application of 1μM SCH23390 delayed the onset of 1μM MeHg- induced [Ca2+]i elevation in both 1st phase ($t(4) = 6.623$, $p < 0.05$) and 2nd phase ($t(4)= 2.884$, $p <0.05$). Raclopride (1μM) also delayed the onset of 1μM MeHg- induced [Ca2+]i in both 1st phase ($t(35) = 3.322$, $p <0.05$) and 2nd phase ($t(35) = 4.256$, $p < 0.05$). The effect of raclopride was also replicated in undifferentiated PC12 cells which indicated the 1μM Raclopride delayed the onset of 2μM MeHg- induced [Ca2+]i elevation in both 1st phase ($t(4) = 3.735$, $p <0.05$) and 2nd phase ($t(4) = 3.874$, $p < 0.05$). These results suggest that acute exposure to MeHg perturbed DA-regulated [Ca2+]i elevation. MeHg may act as D1R activator and D2R uncompetitive inhibitor. Consequently, MeHg could overly stimulate neurons due to the imbalance of excitation and inhibition leading to loss of [Ca2+]i homeostasis, and eventual cell death. Besides, these data implicates MeHg potentially affecting DA signaling which regulates the motor control circuit.

Disclosures: D. Wiwatratana: None. **W.D. Atchison:** None.

Poster

757. GPCR II

Location: Hall A

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Program#/Poster#: 757.04/A88

Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant DA037255

Start up funds from Howard University to CMF

Title: Transactive response DNA binding protein 43 modulation of Cannabinoid type 1 receptor trafficking and signaling

Authors: *A. G. ROBINSON[1], M. R. DESHOTELS[2], P. WEED[2], B. OGUNLADE[1], P. WINSAUER[2], J. J. GUIDRY[2], C. M. FILIPEANU[1];
[1]Pharmacol., Howard Univ., Washington, DC; [2]Pharmacol. and Exptl. Therapeut., Louisiana State Univ., New Orleans, LA

Abstract: Mutations in transactive response DNA binding protein 43 (TDP43), a transcriptional repressor, lead to formation of cytosolic aggregates in neuronal cells, pathological characteristics observed in Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Lobar Degeneration (FTLD), two major progressive neurodegenerative diseases which are currently missing a reliable therapy. Activation of cannabinoid type 1 receptor (CB1R) has been proposed for the treatment of two other major neurodegenerative disorders, Multiple Sclerosis (MS) and Parkinson's Disease (PD). Currently, the possible therapeutic role of cannabinoid receptors in ALS and FTLD is under debate. In humans, CB1R is expressed as three different isoforms, with the lesser prominent subtypes CB1AR and CB1BR being different in the composition of the N terminus compared to the widely expressed CB1R. To identify novel molecular chaperones involved in CB1R trafficking and signaling, we performed a proteomic analysis in transfected HEK293T cells in similar manner as previously described by us. Surprisingly, only one protein, TDP43 was found to interact preferentially with CB1R over CB1AR. This differential interaction was confirmed in co-immunoprecipitation experiments. Interestingly, CP55940, a CB1R agonist, further increased the interaction of CB1R and TDP43. Similar interactions between endogenously expressed CB1R and TDP43 were found in crude rat spinal cord. TDP43 overexpression in HEK293T cells also enhanced CB1R ubiquitination to similar extent as CP55940 stimulation. Further, in HEK293T cells, overexpression of TDP43 significantly decreased CB1R cell surface expression as determined by radioligand binding and ELISA experiments, although it did not change the total cellular receptor levels. This diminished plasma membrane localization of CB1R resulted in reduced effects of CP55940 on cAMP and P-ERK1/2 cellular levels. In contrast, TDP43 overexpression enhanced the effects of CB1R stimulation on P-CREB levels. The same results were obtained after TDP43 overexpression in Neuro-2A cell line on endogenous CB1R localization and signaling. Confocal microscopy experiments in CB1R transfected HEK293 and spinal cord motor neurons demonstrated co-localization of TDP43 and CB1R in heat shocked cells (42^{o}C), but not at physiological temperature. The present results are the first demonstration that TDP43 is a molecular chaperone of CB1R, modulating intracellular receptor trafficking and cellular responses to cannabinoid

ligands. In addition, our data may serve as cellular and molecular basis to better understand the role of CB1R in the patho-physiology of ALS and FTLD.

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Poster

757. GPCR II

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 757.05/A89

Topic: B.03. G-Protein Coupled Receptors

Title: Interplay between serotonergic and L1-mediated signaling in regulation of neuronal morphology and functions

Authors: *D. GUSEVA[1], Y. SCHILL[1], B. MONIKA[2], J. WLODARCZYK[2], E. PONIMASKIN[1];
[1]Hannover Med. Sch., Hannover, Germany; [2]Nenski Inst., Warsaw, Poland

Abstract: Stress-related disorders are shown to be associated with functional disturbance of neuronal adhesion molecule L1. The L1-mediated neuronal migration, development, and regeneration based on homo/ heterophilic L1 interactions seems to be depended on presentation of L1 either as a membrane-bound form or as a proteolytic fragments. We have identified the neuronal L1 as a proteolytic substrate for the matrix metalloproteinase-9 (MMP-9) and demonstrated that L1 fragments generated by MMP-9 cleavage are involved in spine formation in dissociated hippocampal neurons. Together with the observation that the L1 can initiate neurite outgrowth via phosphorylation of actin-binding protein cofilin, this data suggests that MMP-9-mediated proteolysis of L1 might be involved in L1-initiated signaling pathway regulating actin rearrangement in neurons. Serotonergic system has been identified as crucially important to the pathophysiology and the treatment of mood disorders. Neurotransmitter serotonin (5-HT) is involved in neurite outgrowth, growth cone motility and synaptogenesis, and operates via activation of multiple 5-HT receptors. Here we focused on the 5-HT4 receptor (5-HT4R). In the mammalian brain this receptor contributes to regulation of learning and long term memory and is involved in various central and peripheral disorders, including neurodegenerative disease and depression. In our preliminary results we have shown that stimulation of 5-HT4R induces the release of enzymatically active MMP-9 in hippocampal neurons, where 5-HT4R and L1 are tightly co-localized at the synapses. These results demonstrate that 5-HT4R might regulate L1 shedding in an MMP-9-dependent manner, thereby modulating the

homo/heterophilic interaction and paracrine function of L1. We have previously shown that 5-HT4R stimulation results in activation of the small GTPase RhoA, leading to cell rounding and neurite retraction. In our preliminary experiments we have also demonstrated that this effect can be mediated by phosphorylation of cofilin. Thus, cofilin may represent a common downstream effector for both 5-HT4R and L1 suggesting that 5-HT4R, MMP-9 and L1 belong to the same signaling module involved in regulation of neuronal morphology. Taken together, our results demonstrate that 5-HT4R might regulate L1 shedding in an MMP-9-dependent manner, and can thus represent a novel molecular mechanism by which serotonin can regulate the formation and plasticity of neuronal networks and a novel targets for pharmacological intervention into stress-related disorders such as depression.

Disclosures: D. Guseva: None. **Y. Schill:** None. **B. Monika:** None. **J. Wlodarczyk:** None. **E. Ponimaskin:** None.

Poster

757. GPCR II

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Program#/Poster#: 757.06/A90

Topic: B.03. G-Protein Coupled Receptors

Title: Expression analysis of the orphan receptor Gpr139 in the mouse brain

Authors: *A. W. HARRINGTON, S. W. SUTTON, P. BONAVENTURE, C. LIU, T. LOVENBERG;
Janssen R&D, San Diego, CA

Abstract: GPR139, also known as GPRg1 or PGR3, is an orphan GPCR whose mRNA expression in mouse brain has been characterized previously using *in situ* hybridization techniques. Because of potential non-specificity often observed with riboprobes in certain brain regions, we sought to develop new tools to more accurately characterize GPR139 receptor expression and protein localization. A specific rabbit polyclonal antibody was generated to GPR139 using the N-terminus of the receptor as an antigen. In addition, two mouse lines were used to identify GPR139 mRNA-expressing neurons: a lacZ knockin in which the lacZ gene replaces the GPR139 locus; and an EGFP knockin, in which EGFP replaces the GPR139 locus. Using these tools combined with immunohistochemistry, we have confirmed GPR139 expression in two brain regions also shown by *in situ* hybridization: the medial habenula and the lateral septum. Conversely, several regions of the brain positive for expression by *in situ* hybridization did not confirm using these tools. These results provide a clearer picture of the brain regions and

location of GPR139 expression. Subsequent work is aimed at characterizing the identity of GPR139 expressing neurons and understanding the physiological role of the receptor.

Disclosures: A.W. Harrington: None. **S.W. Sutton:** None. **P. Bonaventure:** None. **C. Liu:** None. **T. Lovenberg:** None.

Poster

757. GPCR II

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Topic: B.03. G-Protein Coupled Receptors

Support: HI13C0423

Title: Olfactory marker protein regulates glucagon secretion in mouse pancreatic αTC1-9 cells

Authors: *Y. CHO[1], C. KU[1], N. KANG[2], H. LEE[3], J. KOO[2], E. LEE[1];
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Abstract: Olfactory marker protein (OMP) is highly expressed in olfactory as well as non-olfactory tissues, such as testis, blood vessel, and pancreas. In this study, we evaluated the role of OMP on glucagon secretion from pancreatic islet. The expression of both OMP and glucagon were increased in high glucose treated αTC1-9 cells as assessed using RT-PCR. Moreover, high throughput RNA sequencing showed that OMP and some specific olfactory subtypes were increased in high fat diet induced diabetic rat compared with those of standard diet fed BL6 mice. OMP expression in the pancreatic α-cells was more prominent in diabetic patients compared with that in normal subjects. Furthermore, silencing the OMP using the si-RNA transfection reduced glucagon secretion in αTC1-9 cells despite of high glucose treatment. Our findings demonstrate that OMP regulates glucagon secretion in α-cells of the mouse pancreatic islets, suggesting that OMP and its related olfactory receptors (ORs) may be an important therapeutic target for metabolic diseases.

Disclosures: Y. Cho: None. **C. Ku:** None. **N. Kang:** None. **H. Lee:** None. **J. Koo:** None. **E. Lee:** None.

Poster

757. GPCR II

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Topic: B.03. G-Protein Coupled Receptors

Support: S.D. and J.-F.L. are Postdoctoral Fellow and Research Director of the ‘‘Fonds National de la Recherche Scientifique’’ (F.R.S-FNRS) of Belgium

Fonds Léon Frédéricq of the Faculty of Medicine of the University of Liège

Title: A hydrogen bond in 5-HT1A/D4 selectivity of WAY-100635 analogues: in silico and experimental studies

Authors: *J.-F. LIEGEOIS[1], S. DILLY[2,3];
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Abstract: WAY-100635 is a prototypical antagonist of 5-HT1A receptors and has been used widely as a pharmacological probe to investigate the distribution and function of these receptors (1). However WAY-100635 also displays affinity and activity at D4 dopamine receptors, and that "off-target" activity confounds its use in pharmacological studies, particularly when both receptors are present (2). In this context, a previous study explored various chemical modifications of the WAY-100635 structure and revealed analogues with improved 5-HT1A versus D4 selectivity while others presented higher D4 receptor affinity (3). In order to rationalize this increase in D4 affinity, a recent study combining in silico analysis and mutagenesis was conducted and revealed the key role of a hydrogen bond in the interaction of quinoxaline derivatives with a serine residue (S 7.36) of the D4 receptor binding site (4,5). To further confirm the importance of this hydrogen bond, newly synthesized aza analogues of WAY-100635 have been tested in an *in vitro* binding assay using both the native and the S7.36A mutant D4 receptors. These investigations validate the preliminary data but also precise the right position of the nitrogen atom for the formation of the hydrogen bond. References: (1) Forster et al,. Eur J Pharmacol 1995, 281, 81; (2) Chemel et al., Psychopharmacology (Berl) 2006, 188, 244; (3) Mangin et al., Bioorg Med Chem Lett 2012, 22, 4550; (4) Dilly and Liégeois, Poster presented at the 27th JFBP meeting, Lille (F), June 2013; (5) Dilly and Liégeois, Poster presented at MedChem 2014, Braine-l’Alleud (B), November 2014

Disclosures: **J. Liegeois:** None. **S. Dilly:** None.

Poster

757. GPCR II

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 757.09/A93

Topic: B.03. G-Protein Coupled Receptors

Support: NIH Grant MH101679-02

Title: Gβγ binds to the extreme C-terminus of SNAP-25 to mediate the action of Gi/o-coupled GPCRs

Authors: *Z. ZURAWSKI[1], S. RODRIGUEZ[2], K. HYDE[1], S. ALFORD[2], H. HAMM[1]; [1]Pharmacol., Vanderbilt Univ., Nashville, TN; [2]Biol. Sci., Univ. of Illinois at Chicago, Chicago, IL

Abstract: Gi/o-coupled G-protein coupled receptors (GPCRs) can exert an inhibitory effect on vesicle release through several G-protein driven mechanisms, more than one of which may be concurrently present in individual presynaptic terminals. The synaptosomal-associated protein of 25 kDa (SNAP-25) is a key downstream effector of G protein betagamma (Gβγ) subunits. It has previously been shown that proteolytic cleavage of SNAP-25 by botulinum toxin A (BoNT/A) reduces the ability of Gβγ to compete with the calcium sensor synaptotagmin 1(Syt1) for binding to SNAP-25 in a calcium-dependent manner. These truncated SNAP-25 proteins sustain a low level of exocytosis, but are unable to support serotonin-mediated inhibition of exocytosis in lamprey spinal neurons. Here, we generate a SNAP-25 extreme C-terminal mutant that is deficient in its ability to bind Gβγ while retaining normal calcium-dependent Syt1 binding to SNARE and vesicle release. The SNAP25Δ3 mutant, in which residue G204 is replaced by a stop codon, features a partial reduction in Gβγ *in vitro* as measured by the Alphascreen protein-protein interaction assay as well as a partial reduction in the ability of the lamprey 5HT1b-type serotonin receptor to reduce excitatory postsynaptic current (EPSC) amplitudes, an effect previously shown to be mediated through the interaction of Gβγ with SNAP-25. Syt1 binding to SNAP25Δ3, as measured by GST-pull downs, was not different from wild-type. Next, to begin characterization of the potential pathophysiological roles of the Gβγ-SNAP25 interaction, we produced a transgenic mouse containing the SNAP25Δ3 mutation in the wild-type Snap25 locus utilizing the CRISPR/Cas9 reaction. Preliminary characterization of the mouse with regards to viability, metabolic, neurological and secretory phenotypes are ongoing. We conclude that the extreme C-terminus of SNAP-25 is a critical region for the Gβγ-SNARE interaction.

Disclosures: **Z. Zurawski:** None. **S. Rodriguez:** None. **K. Hyde:** None. **S. Alford:** None. **H. Hamm:** None.

Poster

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Topic: B.03. G-Protein Coupled Receptors

Support: NIDA Training Grant 2T32DA00727821

NIDA DA035577

Title: Distinct signaling cascades underlie 5-HT6 receptor regulation of neuronal morphology

Authors: ***A. J. LESIAK**, M. BRODSKY, J. F. NEUMAIER;
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Abstract: 5-HT6 serotonin receptors can modulate cognition and emotional behaviors, including anxiety, depression, habitual behaviors and reward learning. The 5-HT6 receptor is an excitatory GS-coupled metabotropic receptor that is found almost exclusively in the brain, most abundantly in the striatum, cortex, and hippocampus. Interestingly, 5-HT6 receptor protein is restricted to primary neuronal cilia unless it is heterologously expressed overabundantly, in which case it spills out into the cell membrane. The primary cilium is thought to act like an antenna, receiving chemical and mechanical signals from the surrounding extrasynaptic environment. Since primary cilia may play a critical role in many disorders, including Huntington's and Alzheimer's disease, they may represent a novel therapeutic target for neurocognitive disorders. However, little is known about the mechanisms by which primary cilia regulate neuronal function. The 5-HT6 receptor is known to stimulate two distinct signaling pathways, the canonical cAMP-dependent signaling cascade and the Fyn kinase/Cdk5 signaling pathway. Recently, 5-HT6 receptor antagonism and inhibition has been shown to decrease cilia length in primary neuronal cultures. Additional evidence suggests that strong heterologous overexpression of 5-HT6R can stimulate neurite outgrowth in cell lines via Cdk5 and CDC42 activation. In the present study, we used mature primary neuronal cultures from wild-type and 5-HT6 knockout mice to examine the role of 5-HT6R signaling in neuronal morphology, taking care to avoid excessive heterologous expression so that 5-HT6R remains restricted to the primary cilia as seen with the endogenous receptor. Preliminary data suggests that agonism of endogenous 5-HT6R stimulates an increase in dendritic outgrowth and branching. Likewise, rescue of 5-HT6R expression in 5-HT6R-KO

neurons is sufficient to increase dendritic outgrowth relative to 5-HT6R-KO neurons transfected with empty vector. Expression of a Gs-coupled signaling 5-HT6R mutant was also able to stimulate dendritic outgrowth in 5-HT6R-KO neurons, while expression of FynKinase-signaling deficient 5-HT6R mutant did not. Ongoing experiments will attempt to further dissect the role of these 5-HT6R-dependent signaling events in primary neuronal cilia on cilia and dendritic morphology.

Disclosures: **A.J. Lesiak:** None. **M. Brodsky:** None. **J.F. Neumaier:** None.

Poster

757. GPCR II

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Topic: B.03. G-Protein Coupled Receptors

Support: Regione Autonoma della Sardegna, LR7/2007-CRP10810/2012

Fondazione Banco di Sardegna. Italy

Title: The atypical antidepressants mianserin and mirtazapine induce ERK1/2 signaling and anti-apoptotic effects through activation of the lysophosphatidic acid LPA_1 receptor in mouse hippocampal HT22 cells

Authors: ***M. C. OLIANAS**, S. DEDONI, P. ONALI;
Univ. Cagliari, Monserrato, Italy

Abstract: A large body of evidence indicate that the bioactive phospholipid lysophosphatidic acid (LPA) affects neurogenesis, synaptic plasticity and anxiety-related behaviour by activating specific G-protein coupled receptors, termed LPA_{1-6}, which are expressed in the developing and adult brain. However, relatively little is known on whether the LPA receptor system can be targeted by drugs used to treat neuropsychiatric diseases. We have previously reported that different antidepressants promote growth factor receptor transactivation and cell proliferation in CHO-k1 fibroblasts and glia cells. In the present study, we show that in immortalized mouse hippocampal HT22 cells the atypical antidepressants mianserin and mirtazapine trigger ERK1/2 phosphorylation and protect against apoptosis through LPA_1 receptors. ERK1/ 2 phosphorylation induced by acute exposure to either mianserin, mirtazapine or LPA was inhibited by cell pre-treatment with pertussis toxin, indicating the involvement of G proteins of the $G_{i/o}$ family. LPA, mianserin and mirtazapine also promoted the phosphorylation of the transcription factor CREB,

a downstream effector of ERK1/2 signaling. Cell treatment with either AM966, a selective LPA_1 receptor antagonist, or Ki16425, which preferentially blocks LPA_1 and LPA_3, significantly inhibited ERK1/2 and CREB phosphorylation elicited by mianserin and mirtazapine. Serum withdrawal-induced apoptosis of HT22 cells was markedly attenuated by either LPA, mianserin or mirtazapine, as indicated by the decreased cell death, decreased percentage of annexin V-positive cells, inhibition of pro-caspase activation and poly-(ADP ribose) polymerase cleavage. AM966 reduced the protective effects of mianserin, mirtazapine and LPA against HT22 cell apoptosis. Moreover, cell treatment with the MEK inhibitor PD98059 prevented the anti-apoptotic effect of LPA and mianserin. These data provide further evidence for the involvement of the LPA_1 receptor in the pharmacological action of antidepressants.

Disclosures: **M.C. Olianas:** None. **S. Dedoni:** None. **P. Onali:** None.

Poster

757. GPCR II

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 757.12/A96

Topic: B.03. G-Protein Coupled Receptors

Support: European Community (ZF-Health)

Ecole des Neurosciences Paris Il-de-France (ENP)

Fondation pour la Recherche Médicale (FRM)

Title: Classification of dopamine receptor genes in vertebrates - Nine subtypes in Osteichthyes -

Authors: *K. YAMAMOTO, R. FONTAINE, C. PASQUALINI, P. VERNIER;
CNRS - Paris-Sud University, Neuro-PSI (UMR9197), Gif-sur-Yvette, France

Abstract: Dopamine neurotransmission regulates various brain functions, and at a cellular level, its regulatory roles are mediated by two classes of G-protein coupled receptors (GPCR), D1 and D2 receptor classes. The two classes of dopamine receptors were originally defined on pharmacological ground. Although they both have high affinity for dopamine, D1 and D2 receptor classes are not phylogenetically more related to each other than to other classes of monoamine receptors. In mammals, the D1 receptor class comprises two receptor subtypes (D1 and D5, as known as D1A and D1B in non-human species), and the D2 receptor class comprises three receptor subtypes (D2, D3 and D4). Our phylogenetic analyses of dopamine receptor genes strongly suggest that the common ancestors of Osteichthyes (bony jawed vertebrates) possessed

four subtypes in the class D1, and five subtypes in the class D2. Mammals have secondarily lost almost half of the ancestral genes whereas non-mammalian species kept many of them. Thus the mammalian situation is an exception among Osteichthyes, although the current classification and characterization of dopamine receptors are based on mammalian studies. For meaningful comparison of the data between mammalian and non-mammalian species, we reconstructed an evolutionary scenario of dopamine receptor genes and propose a new classification reflecting correct phylogenetical relationship. In order to simplify one to one comparison of orthologous genes among different vertebrate species, we propose to refer to the four D1-class dopamine receptors as D1, D5, D6 and D7, and to the five D2-class dopamine receptor genes as D2, D3, D4, D8 and D9. Although the nomenclature with numeric suffix reflects only chronologic order of gene discovery and does not take into account the two different dopamine receptor classes, it requires minimal changes from the currently accepted nomenclature. This comparative perspective is crucial to correctly interpret data obtained in animal studies on dopamine-related brain disorders, or more fundamentally, to understand the characteristics of dopamine neurotransmission in vertebrates.

Disclosures: **K. Yamamoto:** None. **R. Fontaine:** None. **C. Pasqualini:** None. **P. Vernier:** None.

Poster

757. GPCR II

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Topic: B.03. G-Protein Coupled Receptors

Support: Barrow Neuroscience Foundation 2014

BNI-UA Seed Fund 2014

Title: Mechanisms of cannabinoid cb2 receptor-mediated modulations in mouse vta dopamine neurons

Authors: ***J. WU**[1], B. LARSON[1], F. GAO[1], Z. XI[2], M. GAO[1];
[1]Barrow Neurolog Inst., Phoenix, AZ; [2]NIDA, Baltimore, MD

Abstract: Growing evidence suggests that brain cannabinoid CB2 receptors (CB2Rs) are importantly involved in several dopamine (DA)-related behaviors and DA-related CNS disorders. We recently reported that brain CB2Rs modulate cocaine's action, including

intravenous cocaine self-administration, cocaine-enhanced locomotion and extracellular DA in the nucleus accumbens in mice. In addition, CB2Rs are recently identified in mouse VTA DA neurons, and activation of CB2Rs in the VTA reduces DA neuron excitability and firing rates in both *in vitro* and *in vivo* preparations. However, the cellular and molecular mechanisms underlying the CB2R-mediated reduction in VTA DA neuronal excitability are unknown. In the present study, we addressed this issue by using patch-clamp electrophysiological recording technology. We first recorded spontaneous excitatory or inhibitory presynaptic currents (sEPSCs, sIPSCs) in VTA DA neurons in midbrain slides. We found that that bath-applied JWH133 (a selective CB2R agonist) significantly reduced the frequency of sEPSCs but not sIPSCs, suggesting that the activation of CB2Rs eliminates presynaptic glutamate release probability, which may in part underlie the CB2R-mediated reduction of VTA DA neuron firing rate. We then used perforated patch-clamp recording in single acutely-dissociated VTA DA neurons to study the effects of JWH133 on the intrinsic membrane properties of VTA DA neurons. We found that bath-applied JWH133 produced an enhancement of M- and A-type K+ channel currents, but failed to alter G-protein coupled inwardly-rectifying K+ (GIRK) current. This effect is mediated by activation of CB2Rs in VTA DA neurons because co-administration of AM630, a selective CB2R antagonist, or genetic deletion of CB2Rs (using CB2R knockout mice) blocked the JWH133-induced potentiation on M- and A-type K+ currents. Collectively, the present findings suggest the important synaptic and intrinsic mechanisms, that CB2R-mediated reduction of presynaptic glutamate release and enhancement of K+ currents appears to play an important role in modulation of VTA DA neuron excitability, DA neuronal firing, DA release in the nucleus accumbens, and subsequent cocaine-seeking behavior.

Disclosures: **J. Wu:** None. **B. Larson:** None. **F. Gao:** None. **Z. Xi:** None. **M. Gao:** None.

Poster

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Topic: B.03. G-Protein Coupled Receptors

Support: NINDS Intramural Program

NIAAA Intramural Program

NCATS Intramural Program

NIDA Intramural Program

Title: Characterization of a novel dopaminergic agonist that displays spatial bias and functional selectively at the D2 dopamine receptor

Authors: *D. R. SIBLEY[1], R. B. FREE[1], J. H. SHIN[2], B. N. MILLER[1], T. B. DOYLE[1], A. E. MORITZ[1], J. L. CONROY[1], T. F. BRUST[3], N. T. SOUTHALL[4], M. FERRER[4], P. DONTHAMSETTI[5], J. A. JAVITCH[5], V. J. WATTS[3], J. L. KATZ[6], G. D. STANWOOD[7], J. W. BERTZ[8], J. H. WOODS[8], K. A. EMMITTE[9], C. W. LINDSLEY[9], V. A. ALVAREZ[2];
[1]Mol. Neuropharm. Section, NINDS-NIH, Bethesda, MD; [2]NIAAA-NIH, Bethesda, MD; [3]Medicinal Chem. and Mol. Pharmacol., Purdue Univ., West Lafayette, IN; [4]NCATS-NIH, Bethesda, MD; [5]Columbia Univ., New York, NY; [6]NIDA-NIH, Baltimore, MD; [7]Florida State Univ., Tallahassee, FL; [8]Univ. of Michigan, Ann Arbor, MI; [9]Vanderbilt Univ., Nashville, TN

Abstract: To identify novel ligands for the D_2 dopamine receptor (D2R), we screened small molecule chemical libraries using high throughput screening. These screens identified a hit compound that selectively activates the D2R in a functionally biased fashion. Chemical optimization resulted in a lead compound (VU207) that exhibits full agonist activity in three different D2R signaling assays: Ca^{2+} mobilization (Gqi5), inhibition of forskolin-stimulated cAMP accumulation (Gi/o), and β-arrestin recruitment. However, VU207 fails to activate D2R-Gβγ-mediated responses including GIRK potassium channel activation and adenylyl cyclase potentiation. Using the β-arrestin recruitment assay, VU207 was also found to exhibit potent D3R antagonism with no functional activity at other dopamine receptors. Further, behavioral paradigms (hypothermia and yawning) indicates that VU207 penetrates the brain and acts as a D2R agonist and a D3R antagonist *in vivo*. Using *ex vivo* brain slices, we investigated the functional activity of VU207 at D2Rs located on dopaminergic neurons. These cells express D2Rs on the cell bodies and dendrites (somatodendritic D2Rs), which activate GIRK channels whereas the D2Rs located on the nerve terminals (presynaptic D2Rs) inhibit dopamine release through activation of Kv1 potassium channels. We found that VU207 failed to activate GIRK currents through somatodendritic D2Rs and, in fact, acted as an antagonist of this D2R response. Notably, in contrast, VU207 acted as an agonist at inhibiting dopamine release via the D2Rs at the nerve terminals. This latter response was absent in tissue from "autoD2R" knockout mice that lack D2R expression in dopaminergic neurons, thus confirming its specificity for D2Rs. These findings suggest that VU207 is a functionally selective agonist and exhibits a unique form of spatial or location bias acting as either an agonist or an antagonist depending on where in the neuron (cell bodies vs. terminals) the D2R is located. It is expected that more cases of location/spatial bias will be observed upon further analyses of receptor-mediated signaling in cells with complex morphologies, especially neurons.

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Poster

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Topic: B.03. G-Protein Coupled Receptors

Support: NIH Fellowship 1F32MH105288

NIH Grant MH56838

Title: Presynaptic strength is increased by platelet activating factor via PKC, elevated intracellular calcium, and synapsin phosphorylation

Authors: *J. W. HAMMOND, S.-M. LU, H. A. GELBARD;
Ctr. for Neural Develop. and Dis., Univ. of Rochester, Rochester, NY

Abstract: Platelet activating factor is an inflammatory phospholipid signaling molecule has been implicated in synaptic plasticity, learning and memory, and neurotoxicity. However, little is known about the intracellular mechanism mediating PAF's physiological or pathological synaptic facilitation. Here we show that the PAF receptor is localized to the synapse. Using fluorescent reporters of presynaptic activity we show that PAF enhances synaptic vesicle release from individual presynaptic boutons by increasing the size of the releasable pool of vesicles. PAF also activates previously silent boutons resulting in vesicle release from a larger number of terminals. The underlying mechanism involves elevated calcium within presynaptic boutons and PKC activation. Furthermore, PAF increases synapsin phosphorylation at sites 1 and 3, (both sites associated with elevated calcium) and increases dispersion of synapsin from the presynaptic compartment during stimulation, freeing synaptic vesicles for subsequent release. In aggregate, these findings provide a conceptual framework for how PAF can modulate synapses during normal and pathologic synaptic activity.

Disclosures: J.W. Hammond: None. **S. Lu:** None. **H.A. Gelbard:** None.

Poster

757. GPCR II

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Topic: B.03. G-Protein Coupled Receptors

Title: G Protein-Coupled Receptor 35 agonists mediate analgesic effects through modulation of hyperpolarization-activated cyclic nucleotide gated channels in rat DRG neurons

Authors: *D. PELLEGRINI-GIAMPIETRO, F. RESTA, A. MASI, M. SILI, A. LAURINO, F. MORONI, G. MANNAIONI;
Univ. of Florence, Florence, Italy

Abstract: Hyperpolarization-activated Cyclic Nucleotide gated (HCN) channels have been recently proposed as the "pacemakers" of pain. HCN2 channel are controlled by cAMP levels and are largely expressed in small Primary Sensory Neurons (sPSN), the majority of which are nociceptors. Intracellular elevation of cAMP levels have been reported to activate HCN-mediated current (Ih), which depolarizes the membrane potential enhancing neuronal excitability and pain sensation. GPR35 is a Gi/o coupled receptor, highly expressed in sPSN, whose activation inhibits adenylate cyclase activity leading to a reduction of intracellular cAMP. We tested the hypothesis that selective GPR35 agonists could exert anti-nociceptive action through the cAMP-mediated modulation of HCN channels in sPSN. Performing patch clamp recordings on cultured rat sPSN isolated from rat dorsal root ganglia, we investigated the effect of GPR35 activation on Ih current and neuronal excitability in control conditions and following stimulation with forskolin (FRK), an adenylate cyclase activator, or prostaglandin E2 (PGE2), a powerful pro-inflammatory mediator. Kynurenic acid, the GPR35 endogenous agonist, and zaprinast, a potent GPR35 synthetic agonist, antagonized the FRK-induced depolarization of resting membrane potential by preventing Ih-mediated depolarization. In the same model GPR35 agonists prevented the PGE2-induced, Ih-mediated depolarization and the resulting increase in overall excitability. Finally, we tested the analgesic effect of the GPR35 agonists in an *in vivo* model of PGE2-induced thermal hyperalgesia. Both GPR35 agonists showed a dose dependent analgesic effect thus confirming the *in vitro* results. Furthermore, we studied GPR35 activation effects in oxaliplatin-induced neuropathy in rats. Our preliminary data showed an increased HCN mediated current in oxaliplatin treated rat sPSN, and a significant antinociceptive effect of ivabradine, the clinically used HCN blocker, on oxaliplatin-induced mechanical allodynia and thermal hyperalgesia. In conclusion, GPR35 activation, through cAMP-dependent inhibition of Ih, leads to reduced excitability of sPSN *in vitro* and exerts a dose-dependent analgesic action *in vivo*, thus representing a promising new target for the development of new analgesic drugs.

Disclosures: D. Pellegrini-Giampietro: None. **F. Resta:** None. **A. Masi:** None. **M. Sili:** None. **A. Laurino:** None. **F. Moroni:** None. **G. Mannaioni:** None.

Poster

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Topic: B.03. G-Protein Coupled Receptors

Title: Dopamine receptor/sodium channel protein complex, a target for antiepileptic mood stabilizers?

Authors: *G. FAKHFOURI, T. DEL'GUIDICEDEL'GUIDICE, A. BARBEAU, M. CHAHINE, J.-M. BEAULIEU;
Psychiatry and Neurosci., Laval Univ., Québec, QC, Canada

Abstract: Background: Although the antiepileptic drugs lamotrigine and valproate are widely prescribed for the management of bipolar disorder, the underlying mechanisms of their mood stabilizing effects are unclear. This hampers the research for the development of newer and safer treatments. Voltage gated sodium channels (Nav) represent a major target of these mood stabilizers. We have previously shown that lithium inhibits a beta-arrestin mediated modality of dopamine D2 receptor (D2R) signalling. Furthermore dopamine receptors have been shown to interact with different type of ion channels. Therefore, we investigated a possible interaction of D2R/Nav. **Methods:** Using an array of protein:protein interaction methods and biochemical assays as well as behavioural paradigms in KO mice and their WT littermates, we explored a potential interaction between Nav and D2R *in vitro* and *in vivo* and the functional consequences. **Results and conclusion:** Our findings demonstrate that the mood stabilizers lamotrigine and valproate inhibit the beta arrestin-2 mediated Akt/GSK-3 signalling downstream of D2R to exert their anti-manic and anti-depressive effects in mice. At the molecular level, Na channels form a complex with D2R leading to alterations in the pharmacological properties of D2R which are sensitive to Nav blockade by lamotrigine and valproate.

Disclosures: G. Fakhfouri: None. **T. Del'GuidiceDel'Guidice:** None. **A. Barbeau:** None. **M. Chahine:** None. **J. Beaulieu:** None.

Poster

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Topic: B.03. G-Protein Coupled Receptors

Support: CIHR grant TGS-109219 to BRS

CIHR Studentship to VS

Title: Sleep deprivation induces changes in 5-HT actions and 5-HT1A receptor expression in the rat hippocampus

Authors: V. SUEN[1], H. AZIZI[1], A. KWOK[1], A. NGUYEN[1], N. KANG[1], R. SOMVANSHI[2], U. KUMAR[2], *B. SASTRY[1];
[1]Univ. British Columbia Fac Med., Vancouver, BC, Canada; [2]Fac. of Pharmaceut. Sci., The Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Sleep deprivation is becoming increasingly common among adolescents, shift workers, and those with busy schedules. Sleep seems to be required for memory consolidation in the hippocampus. Recent studies in our laboratory revealed that hippocampal expression of two prominent G protein-coupled receptors (GPCRs), metabotropic glutamate receptor 1α (mGluR1α) and γ-aminobutyric acid B receptor subunit 1 ($GABA_BR1$), are increased following sleep deprivation. In addition, a hetero-dimerization was observed between the two. Given that GPCRs are known to be dynamically regulated, we investigated whether other GPCRs undergo similar changes. 5-hydroxytryptamine (5-HT) is implicated in modulating sleep and appears to contribute to anxiety, depression and psychosis. 5-HT receptors are largely GPCRs, with $5\text{-}HT_{1A}$ being the most widespread in the hippocampus. The objectives of this study were to examine whether $5\text{-}HT_{1A}$ expression and actions of applied 5-HT in the hippocampus change following sleep deprivation and, if so, whether these changes are reversible. Male Wistar rats were (a) allowed normal sleep (NS), (b) subjected to a 12-hour sleep deprivation (SD), or (c) sleep-deprived for 12 hours followed by a 24 or 48 hour recovery. Stratum radiatum stimulation-induced field excitatory post-synaptic potentials (fEPSPs), in the CA1 pyramidal layer in hippocampal slices, were measured in the presence of bath-applied 5-HT (0 to 40 μM) to construct a dose-response curve. In slices from NS animals, 5-HT depressed the fEPSP in a dose-dependent manner. In slices from SD animals, the depressant action was potentiated. Recovery sleep during a 24 hour period was able to reverse this effect. $5\text{-}HT_{1A}$ expression in the hippocampus was investigated with Western blot and immunohistohemistry. Both methods showed significantly increased expression of $5\text{-}HT_{1A}$ following SD. Almost no reversal of receptor expression was seen following 24 hour recovery sleep and 48 hour recovery sleep resulted in only partial recuperation. In co-immunoprecipitation studies, no hetero-dimerization was observed between mGluR1α or $GABA_BR1$ and $5\text{-}HT_{1A}$. These results indicate that a 12 hour SD results in an upregulation of $5\text{-}HT_{1A}$ receptors and a potentiation of 5-HT's depressant action in the rat hippocampal CA1 area. While there is a recovery from the effect of applied 5-HT in 24 hours, the SD-induced change in $5\text{-}HT_{1A}$ receptors persists. Whether other 5-HT receptors (like $5\text{-}HT_{2A}$) also change with SD and account for the potentiation of 5-HT's action require further

investigation. These results have implications for therapies involving drugs targeting 5-HT pathways.

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Poster

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Program#/Poster#: 757.19/A103

Topic: B.03. G-Protein Coupled Receptors

Title: Persistent adenosine A1 receptor activation within the habenular complex enacts downstream p38 MAPK activation to modulate HCN function and expression and provoke neuronal death

Authors: *D. M. FERGUSON, J. STOCKWELL, X. QIN, F. S. CAYABYAB;
Univ. of Saskatchewan, Saskatoon, SK, Canada

Abstract: In the CNS, the inhibitory adenosine A1 receptor (A1R) is widely regarded as neuroprotective in hypoxia or ischemia, when extracellular adenosine levels increase. We recently reported that prolonged A1R stimulation in hippocampus leads to p38 MAPK-dependent alterations in the excitatory glutamate AMPARs to promote neurodegeneration. Another region where A1Rs are highly expressed is the habenular complex, where hyperpolarization-activated cyclic nucleotide-gated channels (HCNs) are also widely distributed. Since previous studies demonstrated that p38 MAPK regulates HCN function, we hypothesized that prolonged A1R stimulation of habenular complex leads to a p38 MAPK-dependent downregulation of HCNs and a resultant increase in neuronal excitability. In adult male SD rats, following intraperitoneal injections (i.p.) of the A1R agonist CPA (2mg/kg i.p., once daily for 2 days), we observed massive hippocampal and habenular neurodegeneration as shown by Fluoro-Jade B and propidium iodide staining. In both the lateral and medial habenula, this increased neuronal loss after 48hr CPA treatment, was reduced by additional i.p. injections of the A1R antagonist DPCPX (2mg/kg i.p. 1hr after CPA injections). Compared to vehicle-control animals (DMSO in equal values of saline i.p., once daily for 2 days) and CPA + DPCPX treatments, the CPA-treated rats showed reduced HCN1, HCN2, and HCN4 expression in both lateral and medial habenular subnuclei quantified by confocal immunofluorescence microscopy. Moreover, we observed increased activation of p38 MAPK in habenular nuclei in CPA-treated rats, which was prevented by DPCPX co-administration. As increased levels of co-localization between

HCNs and p38 MAPK were also observed in the habenular complex after A1R stimulation, these results suggest a potential role for A1R-mediated downregulation of HCN channels contributing to the observed habenular neurodegeneration. Given the well-established role of the habenular complex in maintaining circadian rhythm and integrating basal ganglia- and cortico-limbic-dependent cognition, these results raise the possibility that pathological elevation of CNS adenosine levels may be sufficient to induce A1R-dependent habenular neurodegeneration and functional deficits to impair such processes.

Disclosures: **D.M. Ferguson:** None. **J. Stockwell:** None. **X. Qin:** None. **F.S. Cayabyab:** None.

Poster

757. GPCR II

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 757.20/A104

Topic: B.03. G-Protein Coupled Receptors

Support: NSERC Grant

Title: Adenosine A1 receptors are required for the adenosine A2A receptor-mediated post-hypoxia synaptic potentiation in the rat hippocampus

Authors: ***X. QIN**[1], J. STOCKWELL[1], D. M. FERGUSON[2], F. S. CAYABYAB[2];
[1]Hlth. Sci., [2]Surgery, Univ. of Saskatchewan, Saskatoon, SK, Canada

Abstract: The mechanism by which adenosine modulates synaptic transmission in hypoxic/ischemic injury remains poorly resolved. Elevation of extracellular adenosine in the hippocampus during ischemia or hypoxia stimulates both adenosine A1 receptors (A1Rs) and A2A receptors (A2ARs), and adenosine-mediated neuroprotection or neurodegeneration are due to A1R and A2AR stimulation, respectively. We recently reported that hippocampal A1Rs and excitatory AMPA receptors (AMPARs) are downregulated through dynamin-dependent, clathrin-mediated endocytosis, while A2ARs are upregulated after a 20-min hypoxic insult or focal cortical ischemia using a pial vessel disruption procedure. Moreover, A1Rs and AMPARs are physically coupled, whereas A2ARs and AMPARs are not. Following hypoxia during normoxic washout, we observed A2AR-dependent synaptic potentiation, and therefore hypothesized that A1R stimulation is required for subsequent adenosine-induced post-hypoxia synaptic potentiation (APSP). We found that a 20-min hypoxia treatment followed by 45-min normoxic washout/reperfusion produced elevated APSP (150-160%), which was abolished by

treatment with either DPCPX (100nM), an A1R antagonist, or SCH442416 (5nM), an A2AR antagonist. Accordingly, using propidium iodide to label dead cells, hypoxia alone caused significant neuronal death, which was significantly reduced by pre-incubation in DPCPX or SCH442416. Hippocampal slices treated with Dynasore (50μM), a dynamin inhibitor, prior to hypoxia blunted the APSP levels (near 120% vs. 150%) and reduced neuronal death, suggesting that prior stimulation of functional A1Rs and subsequent A1R internalization are required for full expression of APSP. A2AR-dependent APSP was accompanied by increased surface expression of GluA1-containing AMPARs. Surprisingly, APSP was not blocked by philantotoxin-74 (50μM) or NASPM (50-100μM), both calcium-permeable AMPAR inhibitors, or by MK-801 (5μM), an NMDAR antagonist, but was abolished by the non-NMDA glutamate receptor antagonist DNQX (10μM). These results suggest a currently unidentified downstream target of the A1R, which is linked to A2AR function; this A1R-A2AR cross-talk contributes to post-hypoxia adenosinergic signaling that enhances synaptic activity and neurodegeneration.

Disclosures: X. Qin: None. **J. Stockwell:** None. **D.M. Ferguson:** None. **F.S. Cayabyab:** None.

Poster

757. GPCR II

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 757.21/A105

Topic: B.03. G-Protein Coupled Receptors

Title: G-protein coupled activation of the volume-activated anion channel in human astrocytoma cells

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[1]Dept Neuroscience, Cell Biology, and Physiol., Wright State Univ., Dayton, OH; [2]Dept Emergency Med., Wright State Univ. Boonshoft Sch. Med., Dayton, OH

Abstract: When osmotically swollen, mammalian cells can regain their normal volume through a process termed regulatory volume decrease (RVD). Volume regulated anion channels (VRAC) have been implicated in controlling cell volume during RVD, but the mechanisms which activate this current are not completely understood. In this study, we examined the role of G protein-coupled signaling via P2Y2 purine receptors for activation of VRAC in osmotically swollen human astrocytoma cells. Methods: Whole cell patch clamp recordings were performed on 1321N1 cells stably transfected to express the human P2Y2 receptor. Cells were sequentially perfused with isoosmotic (290 mOsm) and hypoosmotic (200 mOsm) solutions containing 100

mM CsCl as the major electrolyte. Osmolality was adjusted with added sucrose. The same CsCl concentration was used in the isoosmotic patch electrode solution. Voltage clamp recordings lasting 100 msec were made in 20 mV steps between -100 mV and +100 mV every 30 sec. For some experiments, 100 μM DCPIB, 100 μM suramin, 100 μM ATP, 5 U/ml thrombin, 100 μM carbenoxolone, or 100 μM meclofenamate was added to the perfusate solutions. In others, 1 μg/ml pertussis toxin was added to the patch electrode solution. Results: Hypoosmotic exposure evoked an outwardly rectifying current which inactivated over time at the higher membrane voltages and was inhibited by DCPIB; characteristics ascribed to VRAC. A smaller VRAC current was observed when cells were perfused with a 250 mOsm hypoosmotic CsCl solution. VRAC was not activated by adding ATP or thrombin to isoosmotic solutions; however, adding ATP, but not thrombin, to hypoosmotic solutions increased the VRAC current. VRAC activation was completely blocked by adding suramin to the hypoosmotic solution or pertussis toxin to the patch electrode solution. Carbenoxelone also blocked VRAC activation, but adding ATP or thrombin did not rescue cells from this inhibition. In contrast, meclofenamate had no effect on the VRAC response to hypoosmotic exposure. Discussion: We conclude G protein coupled receptors are necessary for VRAC activation in these human astrocytoma cells. Exogenous ATP enhances the VRAC response in swollen cells but is not sufficient to activate this current in isoosmotic conditions. The lack of an effect by thrombin exposure suggests protease-activated receptors are not coupled to VRAC in these tumor cells. If endogenously released ATP is responsible for VRAC activation via the P2Y2 receptor, it is not effluxed via gap junction hemichannels. Future studies are needed to measure ATP release during hypoosmotic exposure and identify the specific G protein coupled receptor that mediates VRAC activation.

Disclosures: **C.E. Moore:** None. **G. Li:** None. **J.E. Olson:** None.

Poster

757. GPCR II

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Topic: B.03. G-Protein Coupled Receptors

Support: NSERC grant

Title: Neurotoxicity through prolonged adenosine A1 receptor activation: cellular, synaptic plasticity, and behavioral implications in the rat hippocampus

Authors: *J. STOCKWELL[1], D. M. FERGUSON[2], X. QIN[3], Z. MING[1], Z. CHEN[1], F. S. CAYABYAB[4];
[2]Psychology, [3]Hlth. Sci., [4]Surgery, [1]Univ. of Saskatchewan, Saskatoon, SK, Canada

Abstract: Although the adenosine A1 receptor (A1R) is widely accepted as a neuroprotective adenosine receptor in the hippocampus, through inducing synaptic depression during times of metabolic stress, we previously found data to suggest that A1R activation may contribute to widespread neuronal death following focal cerebral ischemia. We first treated acute rat hippocampal slices with the selective A1R agonist CPA, alone or with a subsequent glutamate insult. We found that CPA treatment alone induced significantly more neuronal death than time-matched control slices, and compared to glutamate alone, CPA enhanced the degree of neuronal death caused by glutamate. Using a small tat peptide (YG) designed to prevent A1R-induced AMPA receptor endocytosis, both CPA- and glutamate-induced neuronal death was prevented. We then injected male SD rats with CPA (1mg.kg, i.p. injection daily for 2 days) and saw significant global neuronal death 48 hours following injection, including a high degree of neuronal death within the vulnerable hippocampus. Rats that were injected with the A1R antagonist DPCPX (5mg/kg, i.p.) following CPA treatment showed significantly reduced neuronal death. Additionally, fEPSP electrophysiology experiments on hippocampal slices from CPA-treated rats had impaired chemical LTP (cLTP) induction, whereas DPCPX with CPA-treated rats showed no such impairment. Finally, rats subjected to a small pial vessel disruption (PVD) focal cortical ischemia procedure were tested using a hippocampal-dependent Y-maze behavioral paradigm 48 hours following PVD surgery. PVD caused significantly lower performance compared to sham-operated rats, and animals given DPCPX one hour following PVD surgery had no significant memory deficits. Electrophysiology and post-mortem tissue analysis revealed significantly impaired cLTP and more neuronal death compared to both sham and PVD with DPCPX brains. Together, these results show that persistent adenosine A1R activation induces both neuronal death and memory deficits in the hippocampus. From these studies, we conclude that although the A1R may be neuroprotective in the short term during metabolic stress, prolonged A1R activation triggers an adenosine-mediated excitotoxic potential to ischemia-related neurodegeneration.

Disclosures: J. Stockwell: None. **D.M. Ferguson:** None. **X. Qin:** None. **Z. Ming:** None. **Z. Chen:** None. **F.S. Cayabyab:** None.

Poster

757. GPCR II

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Program#/Poster#: 757.23/A107

Topic: B.03. G-Protein Coupled Receptors

Support: Forschungskommission Heinrich-Heine-University

Title: Time-of-day dependent expression profile of purinergic receptors in the suprachiasmatic nucleus of the mouse

Authors: *J. J. LOMMEN, A. STAHR, M. INGENWERTH, C. VON GALL;
Heinrich-Heine-University, Inst. of Anat. II, Düsseldorf, Germany

Abstract: Background: Purinergic receptors (PR) mediate the signaling of purines such as adenosine triphosphate (ATP) and adenosine. PR subtypes $P2X_{1-7}$, $P2Y_{1-2}$, $P2Y_4$, $P2Y_6$ and $P2Y_{11-14}$ are highly expressed in the brain and have been implicated in learning and memory, locomotor and feeding behavior, and sleep. As all of these functions follow a 24h rhythm, we tested the hypothesis that PRs are expressed in the circadian rhythm generator, the suprachiasmatic nucleus (SCN), in a time-of-day dependent manner. **Methods:** In order to analyze time-of-day dependent fluctuations of PRs, C57Bl/6 (WT) mice, were kept in a standard 12h light/12h dark (12L:12D) cycle. Zeitgeber time (ZT) 0 is defined as the onset of the light phase (6:00 am). Animals were sacrificed in 4 h intervals throughout the day (ZT02, 06, 10, 14, 18, 22). Expression of 15 PR subtypes ($P2X_{1-7}$, $P2Y_{1-2}$, $P2Y_4$, $P2Y_6$, $P2Y_{11-12}$, $P2Y_{13-14}$) were analyzed by immunohistochemistry. In order to test whether time-of-day dependent fluctuations were driven by light as an external stimulus or endogenously driven by the SCN molecular clockwork, additional animals were kept in constant darkness (DD) and sacrificed 2 hours after (CT02) or before (CT22), the former onset of the light phase, respectively. **Results:** Four of 15 PRs, namely $P2X_3$, $P2X_4$, $P2Y_2$ and $P2Y_{12}$, showed a significant time-of-day dependent fluctuation of the immunoreaction signal. Whereas, $P2Y_2$ exhibits peak expression levels during the light/rest phase (ZT02), $P2Y_{12}$, $P2X_3$ and $P2X_4$ show peak expression levels during the dark/activity phase (ZT22). Interestingly, in DD condition expression levels of all PRs were equally low. This suggests a light-dependent regulation of PRs expression in the mouse SCN. **Conclusions:** 1) $P2Y_2$, $P2Y_{12}$, $P2X_3$ and $P2X_4$ are rhythmically expressed in the mouse SCN. 2) This rhythmic expression is externally driven by the light/dark cycle.

Disclosures: J.J. Lommen: None. **A. Stahr:** None. **M. Ingenwerth:** None. **C. von Gall:** None.

Poster

758. GABAergic Synapses and Inhibitory Transmission

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Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NINDS/NIH NS075136

NINDS/NIH NS091144

Klingenstein foundation

NIMH MH086403

NIMH MH091193

Title: Aldehyde Dehydrogenase 1a1 (ALDH1a1) mediates a novel GABA synthesis pathway in midbrain dopaminergic neurons

Authors: *J.-I. KIM[1], S. GANESAN[1], S. X. LUO[2], Y.-W. WU[1], E. J. HUANG[2], L. CHEN[1], J. B. DING[1,3];
[1]Neurosurg., Dept. of Neurosurgery, Stanford Univ., Palo Alto, CA; [2]Dept. of Pathology, Univ. of California San Francisco, San Francisco, CA; [3]Dept. of Neurol. and Neurolog. Sci., Stanford Univ., Palo Alto, CA

Abstract: Midbrain dopamine neurons are an essential component of the basal ganglia circuitry, playing key roles in the control of fine movement and reward. Recently, it has been demonstrated that γ-aminobutyric acid (GABA), the chief inhibitory neurotransmitter, is co-released by dopamine neurons, however, the mechanisms underlying GABA co-release remains unknown. Here we show that GABA co-release in dopamine neurons does not utilize the conventional GABA synthesizing enzymes, glutamate decarboxylases GAD65 and GAD67. Instead, our experiments reveal an evolutionarily conserved GABA synthesis pathway mediated by aldehyde dehydrogenase 1a1 (ALDH1a1). These findings provide new insights into the functional role of GABA co-release in midbrain dopamine neurons, which may be essential for motor control, reward-based behavior and addiction.

Disclosures: J. Kim: None. **S. Ganesan:** None. **S.X. Luo:** None. **Y. Wu:** None. **E.J. Huang:** None. **L. Chen:** None. **J.B. Ding:** None.

Poster

758. GABAergic Synapses and Inhibitory Transmission

Location: Hall A

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Topic: B.07. Synaptic Transmission

Support: National Science Foundation Graduate Research Fellowship Program

NIH grant MH086403

NIH grant MH091193

Title: *In vivo* structure-function analysis of neuroligin-2 at GABAergic synapses of somatosensory cortex

Authors: *A. X. YEE[1], T. SÜDHOF[2,3], L. CHEN[4];
[1]Neurosciences Program, Stanford Univ., Stanford, CA; [2]Mol. and Cell. Physiol., [3]Howard Hughes Med. Inst., [4]Dept. of Neurosurg., Stanford Univ. Sch. of Med., Stanford, CA

Abstract: Autism Spectrum Disorders (ASDs) and Schizophrenia affect 1-2% of the population, and yet the mechanisms causing these neuropsychiatric disorders are largely unknown. Neuroligins (NLs) are trans-synaptic molecules that mediate synapse formation and maturation, and have been found altered in patients of both ASDs and Schizophrenia. Specifically, it is known that one of the NLs, NL2, affects development of GABAergic synaptic transmission. Studies addressing the structure-function of NLs differ as to whether the extracellular versus intracellular domain is sufficient for NL function (Soler-Llavina 2011, Shipman 2011, Futai 2013). This may be in part due to the fact that previous studies of the structural basis for NL function have been done using overexpression or rescues on a knockdown background, which could be subject to caveats such as dimerization of mutant protein with endogenous NL2. We will therefore perform structure-function analysis of NL2 using *in vivo* viral-mediated rescue in a recently-developed conditional knockout (cKO) mouse, where NL2 can be genetically deleted by Cre-mediated excision (Liang 2015). We have confirmed that as in constitutive NL2 knockouts, postnatal deletion of NL2 leads to reductions in GABAergic transmission onto layer 4 stellate/pyramidal cells of somatosensory cortex (S1). AAV-Cre or ΔCre control was delivered by stereotaxic injection at postnatal day 0 (P0) and GABAergic transmission assayed by acute slice recording of miniature IPSCs (mIPSC) and unitary IPSCs at fast-spiking to pyramidal cell synaptically connected pairs (FS-pyr uIPSC). After 21 days of NL2 deletion, mIPSC frequency and amplitude were both decreased, and FS-pyr uIPSC success rate was decreased at higher presynaptic firing rates (10Hz-20Hz). After 40-60 days of NL2 deletion, the magnitude of mIPSC decreases were similar to 21 days of deletion; decreases in FS-pyr uIPSCs success rate were no longer seen, but prominent decreases in amplitude appeared across a range of presynaptic firing frequencies (1Hz-20Hz). Having established that synaptic transmission is altered at mature GABAergic synapses after NL2 deletion, we will next perform rescues with at least a full-length, wildtype NL2, the extracellular domain of NL2, and a chimera containing the extracellular domain of NL2 and the intracellular domain of NL1. Together, these rescue

experiments should (a) verify the ongoing function of NL2 at GABAergic synapses by rescue in a complete knockout background, and (b) shed light onto whether the intracellular or extracellular domain of NL2 is required for this function.

Disclosures: **A.X. Yee:** None. **T. Südhof:** None. **L. Chen:** None.

Poster

758. GABAergic Synapses and Inhibitory Transmission

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 758.03/B2

Topic: B.07. Synaptic Transmission

Support: UZH-FK Grant K-41603-01-01

Title: The gephyrin-interacting protein synArfGEF regulates "mismatched" GABAergic synapses in primary hippocampal neurons

Authors: ***S. FRÜH**, S. K. TYAGARAJAN, J.-M. FRITSCHY;
Inst. of Pharmacol. and Toxicology, Univ. of Zurich, Zurich, Switzerland

Abstract: Postsynaptic differentiation is an important developmental process during synapse formation which is essential for proper synaptic transmission. The accumulation of transmitter-specific receptor, scaffolding and signaling proteins in the postsynaptic density (PSD) depends on transsynaptic signals but is still incompletely understood. *In vivo*, guidance cues as well as transsynaptic adhesion molecules ensure appropriate postsynaptic differentiation corresponding to the presynaptic terminal. However, the absence of such signaling in dissociated neuronal cultures leads to the formation of mismatched synapses, allowing the study of sorting mechanisms between different types of synapses. The guanine nucleotide exchange factor (GEF) synArfGEF was described to be located in GABAergic synapses, although it was first found in the glutamatergic PSD. We report here that synArfGEF can bind to gephyrin, a postsynaptic scaffolding protein specific to GABAergic (and glycinergic) synapses. Coexpression of tagged synArfGEF and eGFP-gephyrin in rat primary hippocampal neurons lead to accumulation of synArfGEF in the GABAergic PSD. Quantitative cluster analysis revealed that coexpression of synArfGEF caused a decreased density of gephyrin and GABAA receptor clusters not apposed to GABAergic terminals. Conversely, overexpression of a catalytic synArfGEF mutant resulted in an increase of VGluT-apposed gephyrin and GABAA receptor cluster density. No change in apposition of GFP-PSD-95 clusters was detected, arguing that synArfGEF specifically regulates the GABAergic PSD. IQ motif in synArfGEF was required both for reduction of mismatched

gephyrin cluster density and for interaction with apocalmodulin. The postsynaptic protein synArfGEF thus regulates GABAergic PSD clustering depending on presynaptic innervation, presumably by activating the small GTPase Arf6. This regulation may be modulated by neuronal activity in glutamatergic synapses as it is dependent on an apocalmodulin-binding motif. Together, our results implicate the postsynaptic protein synArfGEF in differentiation of appropriately matched GABAergic PSDs. Support: UZH-FK grant and SNSF.

Disclosures: **S. Früh:** None. **S.K. Tyagarajan:** None. **J. Fritschy:** None.

Poster

758. GABAergic Synapses and Inhibitory Transmission

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 758.04/B3

Topic: B.07. Synaptic Transmission

Support: The Russian Ministery of Education, the Federal Program (unique identificator - RFMEFI57814X0079)

Title: Temporal and spatial integration of GABAergic and glutamatergic synaptic inputs in dendrites

Authors: *Y. DEMBITCKAYA[1], Y.-W. WU[2], A. SEMYANOV[1];
[1]Univ. of Nizhny Novgorod, Nizhny Novgorod, Russian Federation; [2]Dept. of Neurosurg., Stanford Univ. Sch. of Med., Palo Alto, CA

Abstract: The notion that GABA is main inhibitory neurotransmitter significantly simplifies the repertoire of GABA effects on neuronal computations. In adult brain, GABA can have both depolarizing and hyperpolarizing actions depending on the cell type. The depolarizing GABA inhibits the cell by shunting associated with increased membrane conductance during activation of $GABA_A$ receptors. However, depolarizing GABA can also activate voltage-dependent conductances (e.g. Na^+-channels) bringing the cell to the firing threshold. Which effect will dominate depends on amount of associated $GABA_A$ conductance. If this conductance is high, the shunting inhibition overpowers the excitatory action of GABA. Here we investigated how excitatory or inhibitory actions of GABA depend on temporal and spatial properties of $GABA_A$ receptor mediated membrane depolarization and membrane conductance. We studied the effect of dendritic integration of GABAergic and glutamatergic inputs using mathematical modelling and whole-cell current clamp recordings in CA1 pyramidal neurons or granular cells in mouse hippocampal slices. The intracellular chloride was set to achieve depolarizing effect of GABA.

GABAergic inputs were mimicked by local GABA puff, glutamatergic inputs were mimicked by local glutamate uncaging (uEPSPs). Rapid change in postsynaptic membrane conductance associated with $GABA_A$ receptor activation causes ionic current that gradually polarizes the membrane according to the membrane time constant. When the current (conductance) ceases, the membrane gradually repolarizes. Thus, depolarizing GABA can potentially have excitatory effect during such conductance-free repolarization. However, we could not confirm excitatory action of GABA puff on colocalized uEPSPs during any phase of GABA mediated depolarization. Possibly, the GABA depolarization is relatively small at 'conductance-free' phase to have detectable excitatory action. On the other hand, the conductance is restricted to the location of activated GABAA receptors, while polarization spreads over some distance along the dendrite according to membrane length constant. We found that although GABA puff suppressed colocalized uEPSPs, GABAergic depolarization summed with uEPSP at the distance from the puff. We conclude that depolarizing GABAergic postsynaptic potentials have inhibitory action at the synapse location regardless of coincidence time with EPSP, but excitatory action at the distance from the synapse.

Disclosures: **Y. Dembitckaya:** None. **Y. Wu:** None. **A. Semyanov:** None.

Poster

758. GABAergic Synapses and Inhibitory Transmission

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Topic: B.07. Synaptic Transmission

Support: KAKENHI 15K00413

KAKENHI 24500269

KAKENHI 24240076

Title: A spatio-temporal analysis of the GABAa receptor-dependent and independent membrane potential response to a gamma-band burst stimulus in area CA1 of hippocampal slice: a VSDI study

Authors: *T. TOMINAGA, Y. TOMINAGA;
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Abstract: The gamma-band oscillation occurs in the hippocampus during voluntary behaviors and is thought to relate to learning and the memory process. A stimulation that mimics the

oscillation can induce long-term potentiation in the CA1 region in hippocampal slices, such as a tetanic stimulation and theta burst stimulation. Hence, we aimed to examine the neuronal relevance of the gamma-band neuronal activation with a voltage-sensitive dye (VSD; Di-4-ANEPPS) imaging method. APV (50 μM) was applied to suppress NMDA receptor channels throughout the study. Forty pulses of 100 Hz high-frequency stimulation (HFS) to Schaffer collateral (Sch) caused a long-lasting depolarization in the entire CA1 region, most prominently in the middle of the stratum radiatum (SR), along Sch. The depolarization accompanied the progressive suppression of excitatory postsynaptic potentials (EPSPs) and the supra-recovery of EPSPs after the stimulation. The long-lasting depolarization and the modifications of synaptic transmission were diminished by the application of a GABAa receptor blocker (100 μM PITX). A lasting PITX-sensitive inhibitory postsynaptic current (IPSC) carried by Cl- was recorded from a pyramidal cell with a whole-cell clamp condition. Thus, we concluded that the so-called depolarizing GABA-mediated potential is responsible for the long-lasting depolarization. However, the origin of the IPSC and the cause of the membrane potential reversal from a negative toward a positive direction were not known. To further examine the action of the GABAa response, we applied an AMPA-receptor blocker (10 μM CNQX) and observed 50 ms of hyperpolarization that was followed by long-lasting depolarization. In order to confirm if the potential shift was dependent on the GABAa current, we added PITX. The resulting hyperpolarization took place through the transient depolarization. The inward current not carried by the Cl- current was observed from a pyramidal cell under a whole-cell clamp condition. Low calcium ACSF diminished the transient depolarization, suggesting that the depolarization has a synaptic response. Both hyperpolarization in CNQX + APV and depolarization in PITX + CNQX + APV were more prominent in the perisomatic region than in the SR. The distribution of membrane potential change suggests that the synaptic connections responsible for the inward current have a different distribution than that of the main pathway of Sch. The cellular mechanisms will be discussed.

Disclosures: **T. Tominaga:** None. **Y. Tominaga:** None.

Poster

758. GABAergic Synapses and Inhibitory Transmission

Location: Hall A

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Program#/Poster#: 758.06/B5

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: MEXT/JSPS KAKENHI 19100005

MEXT/JSPS KAKENHI 23800001

Title: Striatal dopamine synapses are neuroligin-2-mediated heterologous contacts between dopaminergic presynapse and GABAergic postsynapse

Authors: *M. UCHIGASHIMA, M. WATANABE;
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Abstract: Midbrain dopaminergic neurons send massive projections to the striatum and play an important role in motor and cognitive functions. Although so-called dopamine synapses are formed on striatal projection type neurons, medium spiny neurons (MSNs), dopamine receptors are distributed extrasynaptically, and the molecular organization at synaptic specializations remains elusive. Here we examined the molecular composition of dopamine synapses in the mouse dorsolateral striatum. The presynapse of dopamine synapses was phenotypically dopaminergic, and further expressed active zone protein CAST, and presynaptic adhesion protein neurexin. On the other hand, the postsynapse consisted of GABAergic postsynaptic proteins including GABAA receptor alpha1, its scaffold protein gephyrin, and postsynaptic adhesion protein neuroligin-2. By combining immunofluorescence with single neuron tracing with lentivirus vectors, we found that dopamine synapses were preferentially formed on denditic elements of MSNs where dopamine receptors D1R and D2R were highly expressed. Among postsynaptic molecules expressed at dopamine synapses, neuroligin-2 could induced the presynaptic differentiation in axons of primary midbrain dopaminergic and striatal GABAergic neurons in culture. By sparse knockdown of neuroligin-2 in the striatum, dopamine synapses significantly decreased with reciprocal increase of GABAergic synapses on MSN dendrites. This suggests that neuroligin-2 controls synapse formation in the striatum by giving competitive advantage to heterologous dopamine synapses over conventional GABAergic synapses. Furthermore, the formation of heterologous dopamine synapses may subserve to increasee the target selectivity and potency of dopaminergic modulation through anchoring dopamine release sites to dopamine-sensing striatal neurons.

Disclosures: M. Uchigashima: None. **M. Watanabe:** None.

Poster

758. GABAergic Synapses and Inhibitory Transmission

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Program#/Poster#: 758.07/B6

Topic: B.07. Synaptic Transmission

Support: NINDS T32 NS07224

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NIMH R01 MH099045

Title: A-type potassium channels regulate the impact of GABAergic inhibition in pyramidal neurons

Authors: *J. T.-Y. CHANG[1,2], M. J. HIGLEY[1,2];
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Abstract: Synaptic integration of glutamatergic excitation and GABAergic inhibition forms the basis of neuronal computation in cortical circuits. A large body of evidence demonstrates that dendritic voltage-dependent conductances play an important role in the spatiotemporal integration of excitatory signals. For example, A-type potassium channels restrict the antidromic propagation of somatic action potentials into distal dendrites. Less is known, however, about the role that potassium channels play in the regulation of inhibitory signaling. Here, we combine electrophysiology, optical uncaging of GABA, and two-photon calcium imaging to investigate the actions of A-type voltage dependent potassium channels on inhibitory GABAergic signaling in layer 5 pyramidal neurons of mouse visual cortex. Our results show that blockade of these channels enhances the somatic inhibitory postsynaptic potential (IPSP) evoked by GABA uncaging on either the apical or basal dendrites. In addition, blockade of these potassium channel increases the impact of inhibition on dendritic calcium signals evoked by back-propagating action potentials. These findings provide additional insight into the cellular mechanisms of synaptic integration in neocortical dendrites, and suggest that neuronal activity may dynamically regulate the efficacy of inhibitory synapses.

Disclosures: J.T. Chang: None. **M.J. Higley:** None.

Poster

758. GABAergic Synapses and Inhibitory Transmission

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Topic: B.07. Synaptic Transmission

Support: GRP Grant (2012R1A1A2006336) from Korean NRF

Title: Evidence that the theory of predictive homeostasis explains the observed strength and decay rate of synaptic inhibition

Authors: J. K. KIM, *C. D. FIORILLO;
KAIST, Daejeon, Korea, Republic of

Abstract: We recently proposed a theory of membrane excitability based on maximizing the information conveyed by spikes from the neuron's point of view (Fiorillo et al., 2014). In order for spikes to be maximally sensitive to the amplitude of synaptic excitation, a large diversity of voltage-gated and synaptic ion channels are proposed to implement "predictive homeostasis" of membrane excitability. The homeostatic ideal is achieved when excitability is such that the peak of an excitatory postsynaptic potential (EPSP) reaches precisely to spike threshold, so that the slightest variation in the amplitude of synaptic excitation determines whether or not there is a spike. This requires that synaptic inhibition and other homeostatic mechanisms accurately predict and counterbalance the amplitude of synaptic excitation, which naturally varies on a timescale of about 1 ms. The theory should allow us to predict the optimal biophysical properties of ion channels and synapses that contribute to homeostasis. Here we characterize the optimal amplitude and decay time of synaptic inhibition. By simulating a single compartment neuron using NEURON software we found the parameter values that minimized 'distance' from the homeostatic ideal at which EPSP peak is at spike threshold. The onset of synaptic inhibition was 1.0 ms after synaptic excitation, as observed experimentally (e.g., Wehr and Zador, 2003; Blitz and Regehr, 2005). Synaptic inhibition maintained homeostasis better than the optimal leak conductance. For synaptic excitation frequencies of 20 to 800 Hz, we found optimal inhibition-excitation peak conductance ratios (I/E) of 0.6 to 2.6 and optimal decay time constants of 2 to 20 ms. As synaptic excitation frequency increased, the optimal I/E increased and synaptic decay time decreased. These theoretical optima are in quantitative agreement with experimental observations. Our results support the theory of predictive homeostasis and illustrate how it can be used to predict biophysical properties.

Disclosures: J.K. Kim: None. **C.D. Fiorillo:** None.

Poster

758. GABAergic Synapses and Inhibitory Transmission

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 758.09/B8

Topic: B.07. Synaptic Transmission

Support: National Institute of Child Health and Human Development

NINDS Competive Fellowship Award

Title: Inhibitory interneurons differentially contribute to spontaneous network activity in the developing hippocampus dependent on their embryonic lineage

Authors: *J. C. WESTER, C. J. MCBAIN;
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Abstract: Spontaneous, internally generated network activity occurs during postnatal development throughout the central nervous system and importantly guides synapse formation. In the hippocampus, which is crucial for learning and memory, this activity is characterized by giant depolarizing potentials (GDPs) during the first postnatal week. GDPs consist of rhythmic bouts of sustained depolarization that last several hundred milliseconds and propagate as a wave. Although immature excitatory pyramidal cells (PCs) are important for GDP generation, GABAergic interneurons also contribute due to a depolarized reversal potential for chloride, which renders them excitatory. Recently, it was discovered that non-overlapping subtypes of interneurons are generated during embryogenesis from the medial and caudal ganglionic eminences (MGE and CGE). In this study, we investigate how MGE versus CGE interneurons are integrated into the hippocampal circuit and contribute to GDPs during the first postnatal week. Using transgenic Nkx2.1-Cre and 5HT3A-Cre mice to target MGE and CGE interneurons, respectively, we performed whole-cell patch recordings in acute slices from postnatal day 5 to 7 mice. To monitor GDPs, we recorded synaptic currents in an interneuron and neighboring PC. We optogenetically silenced MGE and CGE interneurons by expressing cre-recombinase dependent archearhodopsin which generates a non-inactivating, hyperpolarizing current in response to green light. We found that silencing MGE interneurons strongly suppresses GDPs (frequency reduced by 70%), while those that remain are reduced in duration. In contrast, silencing CGE interneurons has a much less dramatic effect on GDP generation (frequency reduced by 30%), with no effect on GDP duration. In order to understand how MGE versus CGE interneurons differentially contribute to GDPs, we performed dual-whole cell patch clamp recordings to test for synaptic connections between interneurons and PCs. Importantly, immature MGE interneurons and PCs are connected with much greater probability (20% MGE to PC; 16% PC to MGE) than CGE interneurons (4% CGE to PC; 2% PC to CGE). Post hoc morphological analysis revealed that MGE interneurons often target the perisomatic region of PCs, while CGE interneurons do so rarely. Our results reveal that interneurons derived from the MGE integrate into the hippocampal circuitry earlier than those from the CGE, synapse near the spike initiation zone, and crucially contribute to GDP generation.

Disclosures: J.C. Wester: None. **C.J. McBain:** None.

Poster

758. GABAergic Synapses and Inhibitory Transmission

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 758.10/B9

Topic: B.07. Synaptic Transmission

Support: Roche RPF-program

SNF, 31003A-153276

Title: Impaired synaptic integration in the Ts65Dn mouse model of Down Syndrome is rectified by negative modulation of α5 subunit-containing GABAA receptors

Authors: *J. M. SCHULZ[1], F. KNOFLACH[2], A. THOMAS[3], M.-C. HERNANDEZ[2], J. BISCHOFBERGER[1];
[1]Dept. of Biomedicine, Univ. of Basel, Basel, Switzerland; [2]Roche Pharma Res. and Early Development, Discovery Neurosci., Basel, Switzerland; [3]Small Molecule Research, Roche Innovation Ctr. Basel, Basel, Switzerland

Abstract: GABAergic hyperinhibition has been suggested to contribute to cognitive deficits in mouse models of Down syndrome (Ts65Dn). Specifically, RO4938581, a negative allosteric modulator selective for the α5 subunit-containing GABAA receptors (α5-NAM) has been shown to improve disturbed synaptic plasticity and spatial learning in Ts65Dn mice (Martinez-Cue et al., 2013). However, the underlying circuit mechanisms are largely unknown. Therefore, we investigated synaptic transmission onto CA1 pyramidal neurons in brain slices from Ts65Dn mice and wildtype (wt) littermates. The ratio of inhibitory postsynaptic currents (IPSC) measured at 0 mV to excitatory PSC amplitude measured at -70 mV after Schaffer Collateral (SC) stimulation was 1.4 ± 0.2 (n=7) in Ts65Dn mice, significantly larger than 0.6 ± 0.1 (n=9) in wt littermates ($P<0.01$). Stimulation of local inhibitory inputs showed that the α5-NAM specifically reduced slow dendritic IPSCs evoked in stratum lacunosum moleculare to 64.4 ±14.4% of the control amplitude, whereas somatic IPSCs evoked in stratum pyramidale remained unaffected. We confirmed the dendritic nature of the α5-NAM-sensitive inputs, using spatially localized GABA release in the presence of TTX from VGAT-channelrhodopsin expressing interneurons. Remarkably, application of the α5-NAM increased excitatory postsynaptic potentials evoked by burst stimulation up to 137.0 ±15.8% (n=8) in TS mice similar to wt mice (148.7 ±14.5%, n=9). Furthermore, impaired theta-burst stimulation-induced LTP in Ts65Dn mice (110.1 ± 3.1%, n=19; wt: 127.1 ± 7.2%, n=14; $P<0.05$) was rectified by acute application of the α5-NAM (122.9 ± 6.2%, n=11). These results demonstrate that α5-NAM counteracts increased dendritic inhibition in Ts65Dn mice to allow for normal dendritic integration of synaptic inputs essential for synaptic plasticity and learning. The work was

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Disclosures: **J.M. Schulz:** None. **F. Knoflach:** None. **A. Thomas:** None. **M. Hernandez:** None. **J. Bischofberger:** None.

Poster

759. Synaptic Integration

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 759.01/B10

Topic: B.07. Synaptic Transmission

Support: NIH R01-MH085974

Title: Reciprocal circuits linking the prefrontal cortex and thalamus

Authors: ***J. J. MARLIN**, A. G. CARTER;
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: The prefrontal cortex (PFC) communicates with multiple brain areas to regulate cognitive function. Bidirectional interactions between the PFC and thalamus play a key role in working memory and attention. While multiple thalamic nuclei are associated with the PFC, the cellular and synaptic properties of these connections are unknown. Here we use anatomical tools, whole-cell recordings, two-photon microscopy and optogenetics to study these circuits. We identify new populations of corticothalamic neurons in the PFC that project to both dorsal and ventral thalamus. We determine how these neurons are differentially innervated by reciprocal inputs from these regions. We next examine the properties of thalamocortical neurons in both dorsal and ventral thalamus that project to the PFC. We also show how these neurons selectively respond to reciprocal inputs from the PFC. Finally, we assess the extent to which this circuitry allows the PFC to serve as a bridge between dorsal and ventral thalamus. Our findings reveal novel neurons and connections that link the PFC and thalamus, which have important implications for our understanding of cognitive processing.

Disclosures: **J.J. Marlin:** None. **A.G. Carter:** None.

Poster

759. Synaptic Integration

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Program#/Poster#: 759.02/B11

Topic: B.07. Synaptic Transmission

Support: NIH R01-MH085974

NIH 1T32NS086750

Title: Excitatory and inhibitory circuits regulating interactions between the PFC and BLA

Authors: *L. M. MCGARRY, A. G. CARTER;
New York Univ., New York, NY

Abstract: The prefrontal cortex (PFC) plays a key role in cognitive and emotional behavior, as highlighted in multiple neuropsychiatric diseases. Control of emotion is thought to critically depend on long-range interactions between the PFC and basolateral amygdala (BLA). Axons from the BLA ramify throughout distinct layers of the PFC, where they are poised to contact multiple neurons. Here we combine whole-cell recordings and optogenetics to study this influence within the adult mouse PFC. We first characterize the properties of different projection neurons that project to distinct downstream nuclei. We determine that BLA inputs make much stronger connections onto corticoamygdala neurons (CA) that project back to the BLA. We then examine the properties of different interneurons that can control circuit activity in the PFC. We show that BLA inputs make unique connections onto parvalbumin (PV) and somatostatin (SOM) interneurons compared to nearby projection neurons. We then assess how these two interneuron subtypes make selective connections onto different types of projection neurons. Finally, we establish the sequence by which BLA inputs activate projection neurons and interneurons in the PFC. Together, our findings reveal the functional properties of both long-range and local circuits in the PFC, with important implications for function and disease.

Disclosures: L.M. McGarry: None. **A.G. Carter:** None.

Poster

759. Synaptic Integration

Location: Hall A

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Program#/Poster#: 759.03/B12

Topic: B.07. Synaptic Transmission

Title: Characterization of inhibitory and excitatory synaptic input recruited by neocortex or amygdala stimulation in perirhinal and entorhinal neurons *ex vivo*

Authors: *J. G. WILLEMS, P. CHAMEAU, T. R. WERKMAN, W. J. WADMAN, N. L. M. CAPPAERT;
Swammerdam Inst. for Life Sci., Univ. of Amsterdam, Amsterdam, Netherlands

Abstract: The insular cortex (neocortical area, NC) and lateral amygdala (LA) both project to the perirhinal (PER) and entorhinal (EC) network. The NC input first recruits all layers of the PER and subsequently the EC. Input from the LA primarily recruits the deep layers of the PER/EC network and subsequently the superficial layers (Willems et al., SfN, 2014-752.03). This study compared synaptic responses and the inhibitory-excitatory (I-E) balance evoked by NC or LA electrical stimulation in PER and lateral EC (LEC) deep layer neurons, in order to address how the PER/EC local circuitry is recruited by NC and LA inputs. Whole-cell voltage-clamp recordings were made in deep layer principal neurons in the PER and LEC in horizontal mouse acute brain slices. Synaptic responses were evoked by electrical stimulation of the NC or LA. NC stimulation evoked a larger peak current amplitude than LA stimulation in both PER and LEC neurons, clamped at -70 mV (PER: NC 268 ± 55 pA, LA 72 ± 21 pA, $p = 0.0015$, $n = 10$; LEC: NC 198 ± 66 pA, LA 66 ± 21 pA, $p = 0.019$, $n = 9$). Furthermore, the latency of NC evoked responses in PER neurons (6 ± 0.4 ms) was smaller than in LEC neurons (13 ± 2.7 ms, $p = 0.001$). LA evoked response latency was similar in PER (9 ± 1.6 ms) and LEC (10 ± 1.4 ms) deep layer neurons. Linear decomposition of the total evoked synaptic conductance separated the excitatory (gE) and inhibitory conductance (gI) in PER and LEC neurons. The NC evoked peak gI and gE were larger than LA evoked conductances in PER and LEC neurons. The latencies of the peak gI and gE evoked by NC stimulation were similar in PER and LEC neurons. The latency of the peak gI evoked by LA stimulation was larger than for the peak gE in PER (gI: 25 ± 4 ms, gE: 15 ± 3 ms, $p = 0.016$), but not LEC neurons (gI: 16 ± 3 ms, gE: 13 ± 2 ms). The I-E balance was defined as the fractional inhibition (I/I+E) calculated from each conductance integrated over the first 75 ms after stimulus. The I-E balance in PER and LEC neurons combined was similar for NC and LA stimulation (I-E balance: NC 70-30 ± 4%, LA 75-25 ± 3%, $n = 19$). Cortical circuits often maintain a critical I-E balance. In PER and LEC neurons that receive both NC and LA input, NC stimulation recruited larger synaptic currents than LA stimulation. NC stimulation sequentially recruited first PER and then LEC neurons, which could be explained by a longer axonal distance for LEC projections. LA stimulation synchronously recruits neurons in the deep layers of PER and LEC. Despite these intricate NC and LA evoked response differences, the recruited I-E balance seems to be maintained on around 73-27%, suggesting that NC and LA inputs recruit a comparable local circuitry in both the PER and LEC.

Disclosures: J.G. Willems: None. **P. Chameau:** None. **T.R. Werkman:** None. **W.J. Wadman:** None. **N.L.M. Cappaert:** None.

Poster

759. Synaptic Integration

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Program#/Poster#: 759.04/B13

Topic: B.07. Synaptic Transmission

Support: NIH R01-MH085974

Title: Differential synaptic connectivity and physiology at layer 5 pyramidal neurons in the prefrontal cortex

Authors: P. G. ANASTASIADES, J. J. MARLIN, *A. G. CARTER;
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: The prefrontal cortex (PFC) is populated by multiple types of pyramidal neurons, which project to diverse cortical and subcortical targets. Recent studies indicate that corticocortical neurons in layer 5 are distinct from adjacent corticothalamic neurons. For example, corticocortical neurons have more compact dendritic morphology and greatly reduced h-current. However, questions remain about the engagement of these neurons by both local and long-range synaptic inputs. Here we use a combination of whole-cell recordings, two-photon microscopy and optogenetics to examine synaptic responses at neighboring corticocortical and corticothalamic neurons in mouse PFC. We find cell-type specific differences in responses to long-range excitatory inputs from both the cortex and thalamus. We also observe different responses to local inhibitory inputs from both parvalbumin (PV) and somatostatin (SOM) expressing interneurons. Finally, we show that h-current plays a critical role in shaping the responses to these different types of synaptic inputs. Together, our findings illustrate several unique functional properties of different populations of pyramidal neurons in the PFC, with important implications for the function and modulation of neural circuits.

Disclosures: P.G. Anastasiades: None. **J.J. Marlin:** None. **A.G. Carter:** None.

Poster

759. Synaptic Integration

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Support: NINDS/NIH NS075136 (J.B.D.)

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NINDS/NIH NS091144 (J.B.D.)

SNI Fellowship (R.L.)

Title: Non-linear synaptic integration on striatal spiny projection neuron dendrites is supported by clustered corticostriatal inputs

Authors: *Y.-W. WU, R. LALCHANDANI, J. B. DING;
Dept. of Neurosurg., Stanford Univ., Palo Alto, CA

Abstract: The dorsolateral striatum of the basal ganglia plays a critical role in action selection and motor control. Striatal spiny projection neurons (SPNs) receive convergent glutamatergic inputs from both motor and sensory cortices, and these inputs form intermingled synapses throughout SPN dendrites. However, how functional inputs from distinct cortical regions are distributed and integrated on the dendrites of SPNs remains largely unknown. Here, we use optogenetic activation of neurons in the primary motor (M1) or primary sensory (S1) cortex combined with two-photon calcium imaging to identify the subcellular distribution of functional corticostriatal synapses. We found that inputs from S1 and inputs from M1 form clusters on SPN dendrites. Simultaneous activation of clustered excitatory inputs using two-photon glutamate uncaging resulted in non-linear integration of excitatory postsynaptic potentials (EPSPs), which could lead to an all-or-none dendritic plateau potential that was dependent on NMDA receptor activation. Our study thus suggests that corticostriatal inputs from functionally relevant cortical areas form clusters onto the dendrites of striatal SPNs to support non-linear synaptic integration in the striatum.

Disclosures: Y. Wu: None. **R. Lalchandani:** None. **J.B. Ding:** None.

Poster

759. Synaptic Integration

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Title: Subthreshold electrical signaling in dendritic spines: modeling and measurements

Authors: M. A. POPOVIC[1], N. T. CARNEVALE[2], *D. ZECEVIC[1];
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Abstract: Thousands of dendritic spines on individual neurons process information and mediate plasticity by generating electrical input signals using a sophisticated assembly of transmitter receptors and voltage-sensitive ion channel molecules. Our understanding, however, of the electrical behavior of spines is limited because it has not been possible to record input signals from these structures with adequate sensitivity and spatiotemporal resolution. Current interpretation of indirect data and speculations based on theoretical considerations are controversial and inconclusive. On the conceptual level, a key question that has not been answered is whether the hypothetical electrical isolation of synapses on spine heads caused by a narrow spine neck is responsible for specific functions which are not supported by synapses on dendrites. Here we use multicompartmental modelling approach based on widely accepted electrical behavior of dendritic cables and experimentally determined dendritic diameters from live neurons to predict the amplitude and the time course of EPSP_spine, EPSP_dendrite, and attenuation ratio AR= EPSP_spine/ EPSP_dendrite for a given synaptic current (I_synapse) for spines at all dendritic locations. Because the calculated dendritic input resistance (Z_dendrite) in the model was much larger than R_neck in most parts of the dendritic tree, the AR was close to unity in these regions. Additionally, because our model shows relatively small spine neck resistance and comparatively high and variable dendritic impedance, the spatial pattern of EPSP_spine amplitudes follows the classical spatial distribution of local dendritic input impedance. To test theoretical predictions by experimental measurements, we developed a technique based on an electrochromic voltage-sensitive dye which can be thought of as a transmembrane optical voltmeter with a linear scale capable of monitoring directly and simultaneously electrical signals from individual spines and parent dendrites. In agreement with modelling predictions, the measurement results demonstrated that synapses on spines are not electrically isolated by the spine neck to a significant extent. Electrically, they behave as if they are located directly on dendrites. Our data agree with old and new evidence based on 2-photon measurements of diffusional resistance of the spine neck as well as with recent 2-photon calcium measurements showing a clear lack of correlation between spine neck lengths and the EPSP rise

time and associated Ca signal in the spine head. At the same time, our data argue against a number of hypothetical functional implications based on large spine neck resistance.

Disclosures: **M.A. Popovic:** None. **N.T. Carnevale:** None. **D. Zecevic:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); RedShirtImaging LLC.

Poster

759. Synaptic Integration

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HBP Grant 604102 awarded to Pr Alex Thomson

Title: A-type K^+ channels impede supralinear summation of clustered glutamatergic inputs in basal and oblique neocortical dendrites

Authors: A. BIRO[1], A. BREMAUD[2], J. FALCK[2], *A. RUIZ[2];
[1]Pharmacol., [2]UCL Sch. of Pharm., London, United Kingdom

Abstract: Dendritic A-type K^+ channels narrow the time-window for synaptic integration. They reduce the amplitude of back-propagating action potentials and participate in several forms of synaptic plasticity. In neocortical layer 5 pyramidal cells, such channels restrain the spread of regenerative potentials and Ca^{2+} transients from apical and tufted dendrites, resulting in strong compartmentalization of signals. However, the functional significance of A-type K^+ channels present in the fine dendrites of cells located in superficial layers of the neocortex is poorly understood. Here, we use two-photon laser-scanning microscopy and glutamate uncaging in *ex vivo* mice brain slices to identify the A-type K^+ channel subtypes involved in signal integration within basal and apical oblique dendrites of layer 3 pyramidal cells. We combine it with computational modeling to examine how changes in dendritic electrical properties and A-type conductance density distribution affect the summation of synaptic potentials. Blocking Kv4.2 and Kv4.3 channels with phrixotoxin-2 enhances the responses elicited by glutamate uncaging at single spines. A millimolar concentration of 4-AP reported to block Kv1.4 has no effect. Both 4-AP and phrixotoxin-2 increase supralinear summation of glutamatergic potentials evoked by synchronous activation of neighboring spines. In a model, the effect of 4-AP is replicated using

either a homogenous distribution or a linear density gradient of dendritic A-type conductance. Thus, Kv4 channels modulate glutamatergic signals at single synaptic inputs whereas Kv1s require the synchronous activation of multiple inputs to regulate the gain of dendritic integration.

Disclosures: **A. Biro:** None. **A. Bremaud:** None. **J. Falck:** None. **A. Ruiz:** None.

Poster

759. Synaptic Integration

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Topic: B.07. Synaptic Transmission

Support: NIH RO1 R01MH101218

ARO W911NF-12-1-0594 (MURI)

Title: Direct electrical recordings from dendritic spines using nano-pipettes

Authors: ***K. JAYANT**[1], J. J. HIRTZ[2], I. J.-L. PLANTE[3], D. M.-T. TSAI[4], W. D. BOER[3], A. SEMONCHE[2], D. PETERKA[2], J. S. OWEN[3], O. SAHIN[2], K. L. SHEPARD[4], R. YUSTE[2]; [1]Electrical Engin. and Biol. Sci., [2]Biol. Sci., [3]Dept. of Chem., [4]Electrical Engin., Columbia Univ., New York, NY

Abstract: Dendritic spines (volume~0.001-0.1 μm^3) are connected to the dendritic shaft through a narrow neck (diameter~0.1μm, length~1μm). Biochemical compartmentalization in spines has been observed by two-photon calcium imaging, however, their function as electrical compartments are still unclear. Neurotransmitter activation of receptors located on the spine head cause excitatory postsynaptic potentials (EPSPs) which eventually shape the downstream dendritic and somatic EPSP. The spine neck could play a major role during this signal processing by rectifying the EPSP as it invades the dendrite while allowing back propagating action potentials and dendritic signals to fully invade the spine. Previous work has supported this hypothesis either computationally or indirectly through optical indicators. The major reason for lack of direct evidence is the small size of the spine head and neck region which makes electrical readout through conventional patch clamp electrophysiology impossible. Here we report direct electrical recordings from dendritic spines using quartz nano-pipette electrodes (diameters ~15-30 nm). We used mouse hippocampal cultures (E18 or P0) and coronal neocortical slices (P7-P15) as experimental preparations. After establishing a conventional somatic patch clamp and backfilling the cell with a dye, dendritic spines (within 100μm from the soma) were located

along dendrites. Carefully compensated nano-pipettes (amplifier input impedance ~1,000GΩ, capacitance compensation ~7-10pF) coated with CdSe/CdS/ZnS quantum dots (QD's) were steered towards the chosen spine. This was entirely carried out under two-photon visualization, rendering the approach applicable in deep scattering tissue. The use of QD's allowed the tip of the nano-pipette to be localized. Upon entry into the spine head via a “touch and buzz” approach, we registered both bAP and spontaneous EPSPs. Resting membrane potentials ranged between -45 and -65 mV (mean ~-53mV). The effect of access resistance and filtering was deconvolved offline to reveal full bAP invasion into the spine. EPSP amplitudes ranged between 15-55mV (mean ~32mV) while simultaneous somatic EPSP amplitudes were very small (<1mV) and, in some cases, non-existent, indicative of strong electrical compartmentalization in the spine head. Additionally, since the impaled nano-pipette interface forms a resistance divider with the spine neck, we calculated neck resistance values through bAP amplitudes to reveal a range ~70-600MΩ (mean ~230MΩ). Our results suggest that dendritic spines behave as separate electrical compartments. **Supported by** NIH RO1 R01MH101218, ARO W911NF-12-1-0594 (MURI)

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Poster

759. Synaptic Integration

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Topic: B.07. Synaptic Transmission

Support: KMR_12-1-2012-0214

Title: Input characteristics of mouse visual cortical neurons measured *in vivo* on the dendritic spine assemblies by fast two-photon imaging using genetically encoded calcium indicators in behaving animals

Authors: ***T. TOMPA**[1,2], G. SZALAY[3], G. JUHASZ[4], L. JUDAK[3], G. KATONA[3], P. MAAK[5], M. VERESS[5], B. CHIOVINI[4], B. ROZSA[3,6];
[1]Med. Univ. of South Carolina, Charleston, SC; [2]Dept. of Preventive Med., Univ. of Miskolc, Fac. of Healthcare, Miskolc, Hungary; [3]Inst. of Exptl. Medicine, Hungarian Acad. of Sci., Budapest, Hungary; [4]Pazmany Peter Catholic University, Fac. of Information Technol., Budapest, Hungary; [5]Dept. of Atomic Physics, Budapest Univ. of Technol. and Econ., Budapest, Hungary; [6]Fac. of Information Technology, Pazmany Peter Catholic Univ., Budapest, Hungary

Abstract: Despite the great efforts of many researchers the functional circuitry of the visual system is still enigmatic. That is especially true regarding the small local functional circuits and the input characteristics of the visual cortical neurons. Knowledge about the incoming and outgoing information and their relation would add a lot to the understanding of visual processing and eventually to the understanding of the general principles of cortical processing. The new possibilities offered by fast 2 photon laser scanning microscopy and the use of genetically encoded neuronal indicators make possible to investigate the above synaptic processing in an unprecedented way to give new insights into the processing. We imaged calcium-indicator expressing neurons *in vivo* in the mouse visual cortex (V1) with two photon laser scanning microscope through a cranial window during active behavior. We mapped dendritic arbors of visual cortical neurons, determining the relationship between spine selectivity, branch selectivity and neuronal selectivity in several neurons in different cortical depths. We have used classical direction-selectivity paradigms, along with other stimulation paradigms. The near-cubic-millimeter scan range, with a high scanning speed (up to 500 pts per kHz), with 470 nm × 490 nm × 2,490 nm resolution in the center core and less than 1.9 μm × 1.9 μm × 7.9 μm resolution throughout the entire scanning volume allows us a very precise functional mapping at different areas and depths of the mouse visual cortex. We also had to develop a high-precision motion artifact compensation algorithm to make possible valid measurement of small neural tissue volumes during activity. Here we present the results, analysis and interpretation of this series of measurements along with the motion-compensation algorithm and its possible uses in *in vivo* experiments with behaving animals.

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Poster

759. Synaptic Integration

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Program#/Poster#: 759.10/B19

Topic: B.07. Synaptic Transmission

Support: 1F31MH106296

Title: The synaptic basis of the pattern-electroretinogram (PERG)

Authors: *N. TORRES JIMENEZ[1], E. GUSTAFSON[2], R. F. MILLER[2];
[2]Neurosci., [1]Univ. of Minnesota, Minneapolis, MN

Abstract: The pattern-electroretinogram (PERG) has been used for clinical diagnosis and scientific studies of retinal function because a patterned visual stimulus is unique in activating retinal ganglion (RGC) and amacrine cells. Although it is generally agreed that the PERG is generated by ganglion cells, the contribution of ganglion cell synaptic receptors has not been resolved with clarity. Our goal is to understand how different levels of D-serine determine the conditions under which the PERG signal reveals an N-methyl-D-aspartate (NMDA) and an Amino-3-hydoxy-5 methyl-4-isoxazolepropionic acid (AMPA) receptor component in the retina. We hypothesize that a reduction in D-serine reflects the NMDAR hypofunction found in schizophrenic patients, and that the lack of D-serine impacts the expression of NMDA receptors in the retina such that abnormities can be observed from PERG. In this study we conducted extracellular recordings from normal (SRWT) and D-serine deprived (SRKO) mice and pharmacologically reduced and enhanced the activity of NMDA receptors with antagonists to evaluate the NMDA component of the PERG. We performed extracellular recordings using an unanesthetized (after perfusion has started), perfused retina eye-cup preparation of male mice between 3 to 5 months of age. The group delineation is based on whether or not they received a pharmacological manipulation. Those mice in the experimental group were treated with D,L-AP7 (NMDAR antagonist) and NBQX (AMPAR antagonist) and D-serine (NMDAR co-agonist), while also blocking inhibitory inputs using a combination of strychnine (glycine receptor antagonist), picrotoxinin (GABAR antagonist) and TPMPA (GABAcR antagonist). Results from our pharmacological studies indicate that the positive component of the PERG, known as the P50 in clinical literature, is largely composed of NMDA and AMPA receptor contributions due to its elimination when the NMDA and AMPRA receptor antagonist were introduced. And, that D-serine deprived mice (SRKO) have a reduced positive component in comparison to wild-type. This study highlights the importance NMDA and AMPA receptors for generation of the positive component of the PERG.

Disclosures: N. Torres Jimenez: None. **E. Gustafson:** None. **R.F. Miller:** None.

Poster

759. Synaptic Integration

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 759.11/B20

Topic: B.07. Synaptic Transmission

Support: Human Frontiers Science Program, Research Grant RGP0036/2014

Title: Astrocytes release glutamate or ATP depending on neuronal activity

Authors: *A. COVELO, A. ARAQUE;
Univ. of Minnesota, Minneapolis, MN

Abstract: Astrocytes are the most abundant cells in the brain and they are actively involved in brain function, playing important roles in synaptic formation, neurotransmitter uptake, water balance and blood flow control. During the last decades, increasing evidence has shown that astrocytes communicate with the pre and postsynaptic terminal, modulating synaptic transmission through the release of gliotransmitters. We have investigated whether a single astrocyte can release different gliotransmitters and characterized the conditions that lead to the release of specific gliotransmitters. We found that that the activation of one astrocyte induce the release of glutamate and ATP, which led to a temporal biphasic modulation (potentiation and depression) of the probability of neurotransmitter release at single CA3-CA1 hippocampal synapses. Activation of astrocytes by high frequency stimulation of Schaffer collaterals, neuron-released endocannabinoids or GABA induced an initial fast and transient (< 3min) synaptic potentiation mediated by glutamate followed by a slower and longer lasting (10-15 min) synaptic depression mediated by ATP/adenosine. The amplitude and time course of the synaptic potentiation and depression depended on the frequency and duration of the neuronal activation. These results indicate that single astrocytes decode neuronal activity pattern and consequently release distinct gliotransmitters that differentially regulate neurotransmission at single synapses.

Disclosures: A. Covelo: None. **A. Araque:** None.

Poster

759. Synaptic Integration

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Topic: B.07. Synaptic Transmission

Support: UTEP Faculty Start-Up Funds 2G12RR008124

University Research Institute Grant (UTEP)

Title: Modulation of sensorimotor gating through PnC afferent structures

Authors: *J. C. CANO, S. A. PACE, K. FENELON;
Biol. Sci., The Univ. of Texas At El Paso, El Paso, TX

Abstract: Sensorimotor gating is a neuronal sensory filtering process that is thought to be governed by central inhibitory mechanisms to help focus attention (Perry and Braff 1994; Swerdlow 1996). Sensorimotor gating is impaired in many psychiatric and neurological disorders including anxiety, schizophrenia, and post-traumatic stress disorder which affect populations worldwide. Patients suffering from these (otherwise unrelated) diseases all show attention deficits that negatively affect education, work, daily life, and social insertion/relations. At the present time, there is no treatment for sensorimotor gating deficits and the attention impairment associated with these diseases. Despite much scientific effort, the brain regions and neural circuits underlying sensorimotor gating are still ill defined, even in healthy subjects. Therefore, the objective here was to further identify the neural elements and connections of the caudal pontine reticular nucleus (PnC), a brain stem structure that is at the core of the sensorimotor gating circuit (Fendt et al., 2001). Better understanding the functional connection of this key brain region under normal conditions might reveal potential therapeutic targets for future medical interventions in diseases associated with attention deficits. We hypothesized that synaptic connections between the PnC and different brain regions essential for sensorimotor gating remained to be identified. To test our hypothesis, we performed a unilateral injection of the retrograde tracer Fluoro-Gold^{TM} (FG) in the PnC of adult mice (N = 5). Following a 1-week recovery period, thin brain sections (50 μm) were made and FG-labelled cell bodies were found, for the first time, in the basolateral (BLA) and the medioventral (MeV) amygdala. To further determine whether the amygdala sends excitatory inputs to PnC neurons, Channelrhodopsin-2 (ChR2) was injected in the amygdala of mice (N = 3), under the control of the CaMKIIα promoter. Extracellular field electrophysiology recordings showed that photostimulation of ChR2-labelled amygdala fibers induced excitatory synaptic responses in acute PnC slices. We conclude that excitatory afferents from the BLA and MeV projecting into the PnC have the potential to modulate sensorimotor gating.

Disclosures: **J.C. Cano:** None. **S.A. Pace:** None. **K. Fenelon:** None.

Poster

759. Synaptic Integration

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Topic: B.07. Synaptic Transmission

Support: NEUROSCAFFOLDS-FP7-NMP-604263

CARBONANOBRIDGE-ERC-2008-227135

PRIN-MIUR n. 2012MYESZW

Title: Nanocomposite biomaterials based on natural polysaccharides for the development of new cell-instructive 3D scaffold driving central nervous system (CNS) reconstruction

Authors: *M. MEDELIN[1], M. PULIN[1], D. PORRELLI[1], A. TRAVAN[1], M. BORGOGNA[1], M. COK[1], I. DONATI[1], E. MARSICH[2], S. PAOLETTI[1], S. BOSI[2], M. PRATO[2], R. SCARDIGLI[3], L. BALLERINI[4];
[1]Life Sci., [2]Univerisity of Trieste, Trieste, Italy; [3]CNR, ROMA, Italy; [4]sissa, Trieste, Italy

Abstract: The merging of technology and material sciences in modern neuroscience promoted significant progress in developing structural scaffolds functionally integrated to the CNS. In recent years we participated to an increased interest and an improved understanding in micro and nano-engineered materials developed to investigate emergent biological adaptive and integrated behaviours in neuronal networks. Our major goal is to develop a new generation of biomaterial-based multifunctional implants able to improve our exploring of fundamental biological phenomena as well as to contribute to biomedical and clinical applications. To this aim, we tested two natural polysaccharides, chitosan and alginate, and a natural-based polymer named chitlac, derived from N-alkylation of chitosan with lactose (D'Amelio et al., 2013), as possible candidates for the production of therapeutic implantable devices. Firstly, we selected a simplified network model, dissociated hippocampal cultures derived from P2-P3 rats, to study neurons interaction when interfaced with different 2D polymer substrates. Biomaterials biocompatibility was proved by immunofluorescence and electrophysiological experiments and, additionally, chitlac-based substrates gave rise to a significantly improved neuronal network reconstruction based on morphological and functional analysis. Moreover, to evaluate the possibility to integrate stem cells as source of neurotrophins in the future 3D bioactive scaffold we tested their impact on the neuronal network construction. Neurons co-cultured with mesangioblasts (MABs) producing BDNF or NGF (Su et al., 2012) developed differently leading to a synaptic activity characterized by increased frequency and amplitude of heterogeneous post-synaptic currents (PSCs). Taken together, these results highlight new strategies to be exploited in order to develop a novel implantable device for the CNS. The further incorporation of nanomaterials such as carbon nanotubes (CNTs; Fabbro et al., 2013) to compensate for natural polysaccharides limits, such as the lack of electrical conductivity, will make these biomaterials even more promising.
D'Amelio et al., 2013 J Phys Chem B 117: 13578-13587; Fabbro et al., 2013 ACS Chem Neurosci 3: 611-618; Su et al., 2012 Cell Transplantation 21: 1613-1627.

Disclosures: **M. Medelin:** None. **M. pulin:** None. **D. Porrelli:** None. **A. travan:** None. **M. borgogna:** None. **M. cok:** None. **I. donati:** None. **E. marsich:** None. **S. paoletti:** None. **S. Bosi:** None. **M. Prato:** None. **R. scardigli:** None. **L. ballerini:** None.

Poster

759. Synaptic Integration

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 759.14/B23

Topic: B.07. Synaptic Transmission

Support: PRIN-MIUR n. 2012MYESZW

NEUROSCAFFOLDS-FP7-NMP-604263

CARBONANOBRIDGE-ERC-2008-227135

Title: Artificial 3D networks as novel tools to investigate plasticity phenomena in reconstructed neuronal networks

Authors: *R. RAUTI[1,2], S. BOSI[2], M. PRATO[2], D. SCAINI[2], L. BALLERINI[3];
[1]SISSA, Trieste, Italy; [2]Univ. of Trieste, Trieste, Italy; [3]sissa, Trieste, Italy

Abstract: The generation of genuine artificial 3D neuronal networks of primary neurons is a current challenge in neuroscience. Two-dimensional cultures of primary neurons have been extremely useful to study the molecular mechanisms modulating neuronal growth and survival, however they represent an oversimplification of the brain's sub regions structure [1]. Recently in our laboratory we succeeded in obtaining rat dissociated hippocampal cultures cultured in a novel biocompatible, elastomeric polymer based, scaffold able to foster 3D organization, in terms of cellular soma location and neuronal processes growth. Our results demonstrated the remarkable ability of the 3D geometry itself to boost signal transmission, when compared to the 2D counterpart, in terms of an increase in event-frequency and synchronization [2]. As a natural consequence of these discoveries we are now reporting on the effect of the 3D organization on long-term potentiation. LTP is of fundamental importance because of its implication in learning and memory as well as other physiological and pathological processes in real brain networks [3], by definition intrinsically three-dimensional. The question we wish to answer is if the 3D configuration could lead to a different way of learning by synaptic networks. For this reason, we have grown hippocampal neurons for 19-21 days-in-vitro and we investigated the induction of functional and morphological plasticity in the 3D networks comparing the Ca2+ signaling response of the network to its 3D organization via confocal and scanning electron microscopy (SEM) reconstructions. Following a brief glutamate application, we found a different reactivity to glutamate and a distinct activation of the different receptor types in the 3D networks when compared to control 2D systems. [1] Limongi T. et al. Small 2013,9,402-12 [2] Bosi S. et al. Sci. Rep. 2015,5,9562 [3] Appleby V.J. et al. J Neurochem. 2011,116, 530-43

Disclosures: **R. Rauti:** None. **S. Bosi:** None. **M. Prato:** None. **D. Scaini:** None. **L. ballerini:** None.

Poster

759. Synaptic Integration

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Topic: B.07. Synaptic Transmission

Support: Chinese Ministry of Science and Technology, Basic Research Program, 2011CB809105

Natural Science Foundation of China, 91232715

NIH, NINDS, CRCNS NS090645

Title: Time translational invariance, the propagation of graded information and the structure of information coding in neural circuits

Authors: *A. T. SORNBORGER[1], Z. WANG[2], L. TAO[3];
[1]Dept Mathematics, Mathematics, Davis, CA; [2]Ctr. for Bioinformatics, [3]Centers for Bioinformatics and Quantitative Biol., Peking Univ., Beijing, China

Abstract: Neural oscillations can enhance feature recognition, modulate interactions between neurons, and improve learning and memory. Numerical studies have shown that coherent spiking can give rise to windows in time during which information transfer can be enhanced in neuronal networks. Unanswered questions are: 1) What is the transfer mechanism? And 2) how well can a transfer be executed? Here, we present a pulse-based mechanism by which a graded current amplitude may be *exactly* propagated from one neuronal population to another. The mechanism relies on the downstream gating of mean synaptic current amplitude from one population of neurons to another via a pulse. Because transfer is pulse-based, information may be dynamically routed through a neural circuit with fixed connectivity. We demonstrate the transfer mechanism in a realistic network of spiking neurons and show that it is robust to noise in the form of pulse timing inaccuracies, random synaptic strengths and finite size effects. We also show that the mechanism is structurally robust in that it may be implemented using biologically realistic pulses. The transfer mechanism may be used as a building block for fast, complex information processing in neural circuits. We demonstrate this by presenting a framework wherein neural information coding and processing can be considered as a product of linear maps

under the active control of a pulse generator. Distinct control and processing components combine to form the basis for the binding, propagation, and processing of dynamically routed information within neural pathways. Using our framework, we construct example neural circuits to 1) maintain a short-term memory, 2) compute time-windowed Fourier transforms, and 3) perform spatial rotations. We postulate that such circuits, with automatic and stereotyped control and processing of information, are the neural correlates of Crick and Koch's zombie modes.

Disclosures: A.T. Sornborger: None. **Z. Wang:** None. **L. Tao:** None.

Poster

759. Synaptic Integration

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 759.16/B25

Topic: B.07. Synaptic Transmission

Title: Precise balance between contrast tuning of excitation and inhibition enables reliable directional selectivity computation in the retina

Authors: *A. POLEG-POLSKY, J. S. DIAMOND;
Synaptic Physiol. Section, NIH/NINDS, Bethesda, MD

Abstract: Retinal direction selective ganglion cells (DSGCs) compare the ratio between synaptic excitatory/inhibitory (E/I) inputs to compute direction selectivity (DS). Their synaptic input is mediated primarily by direct bipolar and feed forward starburst amacrine cells (SACs) pathways. This circuitry can potentially bias synaptic signals in a contrast dependent manner unless the two pathways are not well balanced. Here we show that the E/I ratio in DSGCs is preserved over a wide contrast range. The mechanism that maintains the E/I balance is an enhanced contrast sensitivity of SAC inputs, which compensate for nonlinear synaptic processing in SACs. This phenomenon is mediated by differential contrast tuning between classes of bipolar cells but not within a single bipolar cell. Numerical simulations show that this network arrangement is crucial for an effective DS computation.

Disclosures: A. Poleg-Polsky: None. **J.S. Diamond:** None.

Poster

760. Neuron-glia Interactions

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 760.01/B26

Topic: A.01. Neurogenesis and Gliogenesis

Support: Swedish Research Council Grant 09917

Swedish Parkonsonian Foundation

Umeå University Medical Faculty Funds

Title: The age of the astrocytes affects neuronal growth

Authors: *S. HASHEMIAN[1], J. PHILLIPS[2], S. AF BJÉRKEN[3], I. STRÖMBERG[3]; [1]Pharmacol. and Clin. Neurosci., Umea Univ., Umea, Sweden; [2]Univ. Col. London, London, United Kingdom; [3]Integrative Med. Biol., Umea, Sweden

Abstract: One obstacle with transplantation therapy in Parkinson's disease is the insufficient reinnervation of the host brain by the grafted dopamine neurons. A feasible strategy to overcome this barrier and unravel the underlying mechanisms is to monitor the prospective interaction between the donor fetal tissue and the adult host astrocytes *in vitro*. Therefore, ventral mesencephalic (VM) organotypic tissue cultures from embryonic days (E) 12, E14, and E18 were studied up to 35 days *in vitro* (DIV). In addition, co-cultures of E14 VM tissue and adult green fluorescent protein (GFP) -positive astrocytes were explored. Temporal appearance of tyrosine hydroxylase (TH) -positive nerve fibers from the tissue slice were the first non-glial-associated nerve fibers, followed by the second wave of outgrowth associated with migrated astroglia monolayer formed surrounding the VM tissue. Briefly, the results showed that the non-glial-associated nerve fiber outgrowth was dominant in E14 and absent in E18 cultures. The glial-associated-nerve fiber outgrowth, in E12 and E14 cultures, reached a plateau at 21 DIV. In E18 cultures, TH-positive neurons migrated onto the astrocytic monolayer and displayed short processes. In the co-cultures, the GFP-positive astrocytes were generally located distal to the monolayer of migrated fetal astrocytes; however, a few GFP-positive cells were placed within the fetal astrocytic monolayer and TH-positive neurons migrated towards them. Both the non-glial- and glial-associated-nerve fibers grew onto GFP-positive cells. It is concluded that the glial-associated nerve fibers have limited outgrowth compared to the non-glial-associated ones, while none of them were hampered by the mature astrocytes.

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Poster

760. Neuron-glia Interactions

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 760.02/B27

Topic: A.01. Neurogenesis and Gliogenesis

Support: Australian NHMRC Grant 456027

Australian NHMRC Grant 631552

Australian NHMRC Grant 1048849

NINDS R01 NS34661

Title: Astroglial-mediated remodeling of the interhemispheric midline is exclusive to eutherian mammals and underlies the formation of the corpus callosum

Authors: *I. GOBIUS[1], L. MORCOM[1], R. SUAREZ[1], J. BUNT[1], P. BUKSHPUN[2], W. REARDON[5], W. B. DOBYNS[6], J. L. R. RUBENSTEIN[3], J. BARKOVICH[4], E. H. SHERR[2], L. J. RICHARDS[1,7];
[1]The Univ. of Queensland, Queensland Brain Inst., St Lucia, Australia; [2]Dept. of Neurol., [3]Nina Ireland Lab. of Developmental Neurobiology, Dept. of Psychiatry, [4]Departments of Paediatrics and Neurosurgery, Radiology and Biomed. Imaging, Univ. of San Francisco, San Francisco, CA; [5]Natl. Ctr. for Med. Genet., Our Lady's Hosp. for Sick Children, Dublin, Ireland; [6]Ctr. for Integrative Brain Res., Seattle Children's Res. Inst., Seattle, WA; [7]Sch. of Biomed. Sci., Univ. of Queensland, St Lucia, Australia

Abstract: The corpus callosum forms the primary connection between the cortical hemispheres in the brains of eutherian (or placental) mammals. Congenital absence (or agenesis) of this major fiber tract is a common neurodevelopmental disorder that affects neurological function, yet the etiology underlying this disorder is poorly understood. We identify that a key process required for midline crossing of callosal axons is the remodeling and degradation of the intervening interhemispheric fissure by astroglia during development. *In vivo* gain- and loss-of-function experiments in mice show that this process is initiated by Fgf signaling, which then activates downstream Nfi transcription factors via the Map kinase pathway. Activation of this pathway promotes the transition of radial glia into multipolar astroglia, which intercalate with one another and proteolytically degrade the intervening fibroblast tissue to provide a permissive substrate for callosal axon navigation. Neuroimaging studies suggest that defects in this process and consequent aberrant retention of the interhemispheric fissure are a predominant cause of human callosal agenesis. Furthermore, comparative analyses show that remodeling of the interhemispheric fissure does not occur in acallosal mammals, such as marsupials and

monotremes, strongly suggesting that this glial-mediated process is associated with the phylogenetic origin of the corpus callosum.

Disclosures: I. Gobius: None. **L. Morcom:** None. **R. Suarez:** None. **J. Bunt:** None. **P. Bukshpun:** None. **W. Reardon:** None. **W.B. Dobyns:** None. **J.L.R. Rubenstein:** None. **J. Barkovich:** None. **E.H. Sherr:** None. **L.J. Richards:** None.

Poster

760. Neuron-glia Interactions

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Topic: A.01. Neurogenesis and Gliogenesis

Support: CNPq Universal Grant

Faperj APQ1 Grant

Faperj Temáticos Grant

Title: The radial glia role on angiogenesis in the developing cerebral cortex

Authors: *J. SILVA, M. SIQUEIRA, D. FRANCIS, D. GISBERT;
Inst. de Ciências Biomédicas, Univ. Federal Do Rio De Janeiro, Rio de Janeiro, Brazil

Abstract: Angiogenesis during CNS development is an essential event to provide oxygen and nutrient support to brain tissue. In early stages of the developing CNS, precursor endothelial cells (ECs) from perineural vascular plexus, invade the neural tissue and migrate using the elongated processes of the Radial Glia (RG) neural stem cells as substrate to form the first blood vessels of the brain. Dysfunctional interactions between EC and RG cells impair EC invasion and migration to brain tissues which abrogates blood brain barrier (BBB) development. We previously showed that growth factor TGF-β1 is a potent regulator of RG morphology and differentiation into astrocytes, a cell element of BBB, *in vitro* and *in vivo*. Here we develop a protocol for isolation of murine cerebral ECs to analyze the role of RG-secreted TGF-β1 on angiogenesis in the developing cerebral cortex (Cc) and investigate the role of ECs on RG fate determination *in vitro*. ECs from P7 Swiss mice Cc were isolated and characterized by phase contrast microscopy, immunocytochemistry, RT-PCR, and endothelial tube formation in Matrigel. RG cultures were treated with TGF-β1 and ECs, previously labeled with Cell Tracker dye, were plated on the top of RG cells. In addition, ECs were subjected to Scratch migration assays in presence of RG-conditioned medium (CM). The expression of angiogenesis related genes by ECs, was analyzed

by real time RT-PCR. Further, we performed an Angiogenesis Proteome assay of RG-CM. Finally, we cultivated RG cells in the presence of EC-CM. Our results indicate that ECs isolated using our protocol, express EC markers (PECAM1, vWF, IB4, ZO-1, GLUT1) and form endothelial tubes in Matrigel. TGF- β1-treated RG cells becomes more permissible to EC's invasion/insertion to RG monolayers, as well as the RG-CM promotes a 4x increase in ECs migration on Scratch. Addition of TGF-β receptor inhibitior (SB431542) to RG-CM prevents EC migration. Real time RT-PCR showed that pro and antiangiogenic genes are modulated by the RG-CM (GPR124 and BAI-1, respectively). Further, Proteome identified 11 angiogenesis related proteins in the RG-CM that could be involved in these events. Interestingly, EC-CM treated RG cells showed a robust increment by 7x in GFAP+ cells (astrocytes) numbers. In this work, we established an efficient protocol for ECs isolation from brain tissue. We verified that RG cells promote invasion, migration, tube formation and gene expression by ECs. We also observed that ECs promotes astrocyte differentiation from RG cells, an event essential to ensure BBB formation. Together our results allow us to understand EC-RG interaction dynamics and the underlying molecular aspects involved in BBB formation.

Disclosures: J. Silva: None. **M. Siqueira:** None. **D. Francis:** None. **D. Gisbert:** None.

Poster

760. Neuron-glia Interactions

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 760.04/B29

Topic: A.01. Neurogenesis and Gliogenesis

Title: Increasing functional complexity and maturity of human iPSC-derived neuronal networks *in vitro* by glia co-culture and mixing different neuronal populations

Authors: A.-M. PIELKA, A. VOSS, C. EHNERT, *K. JÜGELT, O. H.-U. SCHROEDER, B. M. BADER;
NeuroProof GmbH, Rostock, Germany

Abstract: There is a high demand in preclinical drug development for novel alternatives to current labor- and animal-intensive behavior tests, and time-consuming brain slice models. *In vitro* neuronal cultures derived from human iPS cells are promising to serve as alternative to animal testing and additionally increasing predictability, selectivity and sensitivity for testing new chemicals and drugs. We aimed to validate hiPSC-derived neurons as a physiologically relevant stem cell-based screening platform incorporating the features of current neurotoxicity

testing in animals and improving current state-of-art by offering higher throughput and higher content. We cultured hiPSC-derived post-mitotic neurons from different commercial sources on multiwell micro-electrode arrays (Axion Biosystems). We co-cultured neurons with human astrocytes or mixed different neuronal populations such as GABAergic and glutamatergic with dopaminergic neurons in order to compare the functional maturation of network activity, survival and success rates after at least 4 weeks *in vitro*. We developed multi-parametric data analysis and pattern recognition methods and compared the functional complexity of hiPSC-derived neuronal activity with primary mouse activity patterns. We show that under certain culture conditions hiPSC-derived neurons functionally mature into networks which initiate complex bursting network activity comparable with those of primary neuronal networks. In conclusion, with our optimized culture protocols, human stem cell-derived neurons have the potential to meet the expectations in replacing current animal-based *in vitro* models or to be used for comparing drug-induced effects between rodent and human background, thus increasing predictability, selectivity and sensitivity, highly demanded for improved drug discovery.

Disclosures: **A. Pielka:** A. Employment/Salary (full or part-time):; NeuroProof GmbH. **A. Voss:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroProof GmbH. **C. Ehnert:** A. Employment/Salary (full or part-time):; NeuroProof GmbH. **K. Jügelt:** A. Employment/Salary (full or part-time):; NeuroProof GmbH. **O.H. Schroeder:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroProof GmbH. **B.M. Bader:** A. Employment/Salary (full or part-time):; NeuroProof GmbH.

Poster

760. Neuron-glia Interactions

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 760.05/B30

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R01 EY024694

E. Matilda Ziegler FNDT AGRMNT

Alfred. P. Sloan FNDNT #00027374

McKnight Endow/Neuroscience Awd

Title: Characterizing Müller glia network assembly in mouse retina

Authors: *J. WANG, J. KAY;
Duke Univ., Durham, NC

Abstract: Astrocytes form a physical network with their arbors that pervades the entire central nervous system. This network engages in signaling among astrocytes, and mediates selective interactions with neurons, synapses, and blood vessels. These interactions have important roles in regulating neuronal and vascular physiology. Indeed, the universal presence of astrocyte arbors throughout both gray and white matter suggests their essential roles in nervous system function. However, the developmental mechanisms that ensure complete astrocyte tissue coverage remain unclear. As astrocytes have largely non-overlapping territories, a phenomenon known as "tiling," one possibility is that they simply grow until they touch their homotypic neighbors. We aim to test whether this homotypic recognition/repulsion model explains glial tissue coverage, and ultimately to develop a system for studying the molecular basis of such recognition. Since mouse retina is more experimentally accessible than brain, we began by asking if Müller glia (MG), the major astroglia-like cell of retina, might be a suitable model to address our aims. MG have a much more complex shape than astrocytes, so an initial question was whether MG, like astrocytes, exhibit tiling. Moreover, because MG traverse all retinal layers and ramify arbors with distinct morphology at each layer, we wanted to know: If MG tile, do they do it at all retinal layers? By utilizing the astroglia-specific Glast-CreER mouse line and a viral "Brainbow" strategy, we obtained multi-color images of adjacent MG that allowed us to delineate cell borders. We then measured the percentage overlap of the neighboring MG arbors and found that they indeed tile, as shown by minimal overlap (less than 5%). Moreover this tiling was found at all retinal levels. We then asked when tiling arises in development. Using a Cre reporter mouse line expressing membrane-targeted fluorescent proteins, we were able to visualize detailed MG morphology and uncover the initial time when they come in contact with one another. Our results set the stage to uncover the cellular and molecular mechanism of glial tiling in the retina, with implications for learning how brain glia form their ubiquitous networks.

Disclosures: J. Wang: None. **J. Kay:** None.

Poster

760. Neuron-glia Interactions

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Topic: A.01. Neurogenesis and Gliogenesis

Support: DFG BO1743/3 (U.B.)

SFB/TRR 1052 (U.B.)

Title: Midline glia express transient receptor potential channel subfamily M member 5 (TRPM5) during embryonic and early postnatal mouse brain development

Authors: *S. WEN, S. KUSUMAKSHI, U. BOEHM;
Inst. of Exptl. and Clin. Pharmacolog, Homburg/Saar, Germany

Abstract: Transient receptor potential channel subfamily M member 5 (TRPM5) is an important downstream signaling component in a subset of taste receptor cells. While TRPM5 has also been detected in extra-oral tissues, the function of non-gustatory TRPM5-expressing cells is less well understood. Interestingly, TRPM5 expression has also been reported in the central nervous system, however the individual cells in the brain that express this ion channel have not been identified. We recently developed a binary genetic strategy to report TRPM5 expression in mice. Specifically, we generated a novel TRPM5-IRES-Cre mouse strain to report TRPM5 expression using a Cre-activated τGFP reporter. To confirm faithful coexpression of τGFP and TRPM5 we generated and validated a new anti-TRPM5 antiserum enabling us to analyze acute TRPM5 protein expression. τGFP cells were found in taste bud cells of the vallate, foliate and fungiform papillae as well as in the palate as expected. We then used the animals to analyze TRPM5 expression in the central nervous system. Surprisingly, we find that TRPM5 expression persists in the ventral part of the mouse midbrain and hindbrain in a subpopulation of midline glial cells during late embryonic stages. These cells then gradually disappear at early postnatal stages and have completely vanished at postnatal day 14. Here we characterize these TRPM5-expressing midline glial cells and investigate their potential function during mouse brain development. To do so we express different tracer molecules in these cells to analyze their communication with other cells during late embryonic and early postnatal mouse brain development.

Disclosures: S. Wen: None. **S. Kusumakshi:** None. **U. Boehm:** None.

Poster

760. Neuron-glia Interactions

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 760.07/B32

Topic: B.11. Glial Mechanisms

Support: NIH NINDS NS076885 (to CD)

American Epilepsy Society Research Grants (to CD)

Title: Distinct roles of GLAST and GLT-1 in regulating cortical network formation and maturation

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Abstract: The excitatory amino acid transporters (EAATs) GLAST and GLT-1 are responsible for the majority of the glutamate uptake in the brain. GLAST is the predominant mode of glutamate transport in the early postnatal brain, and the burden shifts over to GLT-1 as the brain matures. This developmentally timed expression of GLAST and GLT-1 contributes to proper structural and functional maturation of the brain. For example, loss of these transporters during the development of the mouse whisker barrel cortex disrupts its architecture and whisker representation. Our lab has shown that the normal developmental function and expression of GLAST and GLT-1 is altered in a model of cortical malformation. After freeze lesion injury, astrocyte density is decreased, presumably leading to a decrease in the number of available glutamate transporters. The remaining astrocytes have increased glutamate responsive areas and have an altered developmental progression of EAAT reliance. How these developmental changes in glutamate transporters might then influence cortical network organization and connectivity is not fully understood. To better understand the roles of GLAST and GLT-1 in handling extracellular glutamate during development, and whether changes in transporter levels affect neuronal migration and synapse refinement, we will use mice with partial genetic knockdown of the GLAST and GLT-1 genes (GLAST+/- and GLT-1+/-, respectively). These mice are viable and have roughly 68% of wild-type glutamate transporter protein levels when mature. We found that partial loss of GLAST during development leads to an abnormally excitable and epileptiform cortical field EPSP responses at P16-26, a time period after the shift from GLAST to GLT-1. However, we do not see this increased excitability with a partial loss of GLT-1. This hyperexcitability phenotype is similar and not additive to that seen in neonatal freeze lesioning, further suggesting that alterations in glutamate transporters plays a role in freeze lesion pathology. Our preliminary data also shows that glutamate transporter currents in Layer V cortical astrocytes are not different between GLT-1+/- and wild type, but have smaller amplitudes in GLAST+/-. These data suggest that there is a distinct, indispensable role of GLAST during development that prevents the formation of a hyperexcitable network, and that decreased GLAST expression leads to its altered function in the mature brain. Further investigation is required to understand what this specific role of GLAST is during development and how it is different from that of GLT-1.

Disclosures: J. Shih: None. **Y. Yang:** None. **N.C. Danbolt:** None. **C. Dulla:** None.

Poster

760. Neuron-glia Interactions

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Topic: B.11. Glial Mechanisms

Support: Contract # HHSN271201100029C

NS R01 NS065434

Margolis Foundation

Title: Neurodegeneration, gliosis, and glial proliferation in two models of temporal lobe epilepsy

Authors: J. L. LOEWEN[1,2], M. L. BARKER-HALISKI[3,2], E. DAHLE[3], H. WHITE[3,1,2], *K. S. WILCOX[3,1,2];
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Abstract: In the Anticonvulsant Drug Development (ADD) Program, research is ongoing to identify animal models appropriate for the identification of novel compounds more efficacious in the large population of treatment-resistant patients. The corneal kindled mouse is a model of temporal lobe epilepsy (TLE) that allows for the rapid screening of investigational compounds. However, lack of information as to the specific inflammatory pathology resulting from corneal kindling in mice leaves research towards development of ASDs in this model uninformed. Likewise, the Theiler's murine encephalomyelitis virus (TMEV) model of infection-induced TLE may prove to be a useful model for screening, but quantitative assessment of neurodegeneration, glial reactivity, and cell-type-specific proliferation is lacking. Thus, the current study set out to test the hypothesis that these two very different mouse models would display distinctive neuropathological characteristics. C57BL/6 mice were injected intracranially with PBS or TMEV (3 X 105 PFU), monitored for seizures, and sacrificed 4 and 14 d post-injection (n=8 per group). CF1 mice were corneally stimulated until fully kindled, and sacrificed with unstimulated controls 1 d and 7 d after (n=8 per group). Serial 25 μm brain sections from each group were stained with antibodies directed against NeuN to evaluate neurodegeneration, and GFAP and Iba1 to determine the extent of astro- and microgliosis, respectively. In addition, antibodies directed against Ki67 were used to assess proliferation in glial cells. Z-stacks were collected in CA1, cortex, and DG with a confocal microscope and analyzed using ImageJ. In the hippocampus of TMEV-injected mice (4 and 14dpi) both microglia and astrocytes had significantly increased expression of Iba1 and GFAP, respectively; indicative of reactive gliosis. As previously described, there was also a significant degree of cell death in the CA1 region. In

contrast, there was no significant neurodegeneration or activation of microglia in CA1 of corneal kindled mice. Increases in GFAP expression were seen, however, suggesting that astrocytes are reactive in this model. Significant increases in the number of Ki67+ nuclei combined with colocalization analyses demonstrated that there was proliferation of microglia and astrocytes in the DG of TMEV-infected mice at 4 dpi. These results indicate different classes of ASDs could have varied effects on seizures observed in these two models, and the use of multiple mouse models of TLE in drug screening efforts is likely to be beneficial.

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Poster

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Topic: B.11. Glial Mechanisms

Support: NIH Grant 2R25GM060414

RO1 NS078410-01

Title: Immunohistochemical analyses reveal changes in astrocytic density in the dorsal raphe nucleus after stress

Authors: *I. S. NICHOLS[1], C. O. OKERE[2], K. PAUL[3];
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Abstract: The dorsal raphe nucleus (DRN) is an important component of the stress response circuit. In rats, acute stress alters nitric oxide synthase (NOS) activation in the DRN. Specifically, active NOS expression is enhanced in the caudal region. Astrocytes store and release the precursor for NOS to make nitric oxide (NO). Astrocytic organization in the DRN is important because it may help reveal the regulatory role of NOS on stress responses. Glial fibrillary acidic protein (GFAP), a marker for astrocytes, increases in other stress-sensitive brain areas during chronic stress. Our hypothesis is that there will be an increase in GFAP staining as a result of stress, revealing a unique organization among astrocytes. Following acute or chronic stress coronal sections (20 μm-thick) of the DRN from rat brains were stained with GFAP antibody and then visualized with avidin biotin complex and peroxidase (n=3-4). Using Image J,

density measurements were taken by measuring mean gray value for the rostral and caudal subregions. This analysis revealed differences in astrocytic density between acute and chronic stress for both rostral ($p=0.05$) and caudal ($p=0.02$) subregions. Under baseline conditions, astrocytic organization in the rostral DRN was different from the caudal region; the rostral staining was ubiquitous while the caudal staining was localized mostly to the midline and lateral wing regions. Although acute and chronic stress increased astrocytic density throughout the DRN, it did not change the organizational relationship between rostral and caudal regions. To conclude, this unique pattern of astrocyte distribution may suggest functional specialization for astrocytes in the DRN especially as a response to stress.

Disclosures: I.S. Nichols: None. **C.O. Okere:** None. **K. Paul:** None.

Poster

760. Neuron-glia Interactions

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Program#/Poster#: 760.10/B35

Topic: B.11. Glial Mechanisms

Title: Protein levels of cell adhesion molecules in the supraoptic nucleus of 1- and 4-month-old rats: implications for a role in axonal sprouting?

Authors: *P. KUBALL, E. BYE, M. MCCARTHY, A. AL SAEGH, J. ASKVIG;
Concordia Col., Moorhead, MN

Abstract: It has been demonstrated that a young brain can overcome injury by axonal sprouting; however, it is well understood that the mature brain has a reduced capacity for functional or structural reorganization following injury. To this point, following injury, uninjured axons from the supraoptic nucleus (SON) undergo collateral sprouting in the 35-day-old rat, but not in 125-day-old rats. Therefore, it appears that within the SON there are age-related changes that preclude the older rat from recovering following injury. Cell adhesion molecules have been previously demonstrated to play a role in axonal sprouting, both in a stimulatory and inhibitory manner. Thus, we compared protein levels of cell adhesion molecules in the 35 and 125-day-old SON using Western blot analysis. Our results demonstrated that in the 125-day-old SON, there was a significant increase in thy-1 protein levels, which is an anti-sprouting factor that interacts with integrins. Moreover, we determined the protein levels of cell adhesion molecules in the sprouting (35-day-old rat) and non-sprouting SON (125-day-old rat). Our results suggest that the observed increase in thy-1 protein levels in the SON with age may contribute to an environment that prevents axonal sprouting in the SON of an older rat.

Disclosures: **P. Kuball:** None. **E. Bye:** None. **M. McCarthy:** None. **A. Al Saegh:** None. **J. Askvig:** None.

Poster

760. Neuron-glia Interactions

Location: Hall A

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Topic: B.11. Glial Mechanisms

Support: IBRO

Title: Electrophysiological effects of glial inhibition on pyramidal neurons in rat brain slices

Authors: *S.-. DARIANI SAEED[1], M. JANAHMADI[2];
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Abstract: Glial cells play an important role in control of neuronal excitability. However, the cellular mechanism of this effect is not fully determined. In the present study, the electrophysiological alteration induced by glial inhibition in the CA1 pyramidal neurons of hippocampus using whole cell patch clamp recording was examined after application of minocycline. Results indicated that glial inhibition after minocycline inhibition (100μM) causes a significant reduction ($P<0.05$ (in the pyramidal neurons from 1.21±0.5 Hz in control group to 0.098±0.01 Hz in the presence of minocycline using whole cell patch clamp recording under current clamp condition, which was associated with an increase in the electrical discharge of cells. Minocycline treatment did not affect the resting membrane potential, but increased the cell input resistance from 82.6M Ω to 104.24M Ω. In addition, minocycline resulted in an insignificant reduction in both the amplitude of post stimulus after hyperpolarization potential and sag voltage evoked in response to depolarizing and hyperpolarizing current pulses, respectively. In summary it seems that glial inhibition causes severe alterations in cell excitability through changes in passive and active properties of hippocampal pyramidal cells.

Disclosures: **S.-. Dariani Saeed:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); receip of drugs. **M. Janahmadi:** None.

Poster

760. Neuron-glia Interactions

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Topic: B.11. Glial Mechanisms

Title: The cytokine IL-1ß is able to diminish amplitudes of cortical spreading depression (CSD) in adult rats

Authors: F. RICHTER[1], J. LEUCHTWEIS[1], A. EITNER[1], E. WEGNER[1], *A. LEHMENKUHLER[2], H.-G. SCHAIBLE[1];
[1]Inst. of Physiol., Univ. Hosp. Jena, Jena, Germany; [2]Pain Inst., Dusseldorf, Germany

Abstract: IL-1ß is thought to play an important pathophysiological role in the brain e.g. in stroke and neurodegenerative diseases. Here we tested, whether IL-1ß influences CSD, a neuronal mechanism of pathological hyperexcitability. We recorded in spontaneously breathing anesthetized adult rats (sodium thiopentone, 100 mg/kg, i.p.) CSD in cerebral cortex with two pairs of glass micropipettes (distance 5-6 mm) at depths of 1200 µm. CSD was elicited by a microinjection of 1 M KCl (tip diameter 5 µm, 100 kPa, 300 ms - 1 s). We administered in one group of rats 50 ng IL-1ß. In another group we applied 500 ng of an IL-1 receptor antagonist together with 50 ng IL-1ß after 30 min pretreatment with the receptor antagonist alone. We compared the effects of IL-1ß with the topical application of 2 µg lipopolysaccharide (LPS) and blocked the IL-1ß receptor as well. To elucidate possible modes of action of IL-1ß, we applied 1 µM of the GABAA receptor antagonist bicuculline topically to the cortical surface for half an hour and applied subsequently IL-1ß. All cytokine applications lasted 4 hours and CSD were elicited every 30 min in the first two hours and then every hour. In a subgroup, the cortices treated with IL-1ß were stained with Evans blue, and we looked for plasma extravasation and for the localization of the IL-1ß receptor. The application of IL-1ß decreased the CSD amplitudes in the treated area down to 55.2±7.4% of controls, but in the untreated area CSD amplitudes decreased only to 85.1±4.9% (mean±SEM, n=6). This decrease could be abolished by coapplication of IL-1ß and the IL-1 receptor antagonist. Interestingly, CSD amplitudes increased after that treatment in the treated area up to 125.8±5.9% of controls, whereas they decreased in the untreated area down to 89.1±8 % (n=4). Application of the receptor antagonist alone resulted in an increase of CSD amplitudes and spontaneously occurring CSD waves. Application of LPS caused a similar decrease of CSD amplitudes as IL-1ß. This decrease could be abolished by coapplication with the IL-1ß receptor antagonist as well. The GABAA receptor antagonist bicuculline slightly increased CSD amplitudes. After coapplication of bicuculline together with IL-1ß CSD amplitudes reached 125.8±5.9 % of controls (n=3). This indicates that inhibitory neurons might be involved in the action of IL-1ß on CSD. Histological observation showed the expression of IL-1ß receptors at neurons and microglia and plasma extravasation in the IL-1ß treated areas. These results suggest that IL-1ß could decrease CSD via the release of GABA and

via plasma extravasation. LPS induces a release of IL-1ß and influences CSD in this way. The plasma extravasation might be harmful for the brain.

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Poster

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Topic: B.11. Glial Mechanisms

Support: NS0889442-01

NS060632-06

Title: HIV-1 mediated disruption of Wnt/β-catenin signaling in astrocytes lead to neuronal injury

Authors: ***V. B. LUTGEN**, C. YU, S. NARASIPURA, L. AL-HARTHI;
Micro/Immuno, Rush Univ. Med. Ctr., Chicago, IL

Abstract: Neuronal injury characterized by synaptodendritic dysregulation and/or apoptosis is a prominent feature of HIV-Associated Neurocognitive Disorders (HAND). Neuronal injury may arise, in part, from impaired function of glial cells. Abnormal astrocyte activity will result in decreased neuroprotection due to increased release of inflammatory mediators, abnormal glutamate cycling and dysregulation of secretory factors critical for astrocyte-neuronal communication. Wnt/β-catenin signaling in astrocytes regulates a number of genes responsible for cell survival, structure and function. Neuronal β-catenin is important for the regulation of dendrite and spine morphology and synaptic activity. We previously showed that inflammatory mediators, HIV infection, and HIV Tat down regulate Wnt/β-catenin signaling in astrocytes. We evaluated here the impact of down regulation of astrocytic β-catenin signaling on neuronal injury. Towards this end, primary human fetal astrocytes (HFAs) were infected with HIVBaL or knocked down (KD) for β-catenin using siRNA and the astrocyte conditioned media (ACM) was added to Lund human mesencephalic (LUHMES) cells, which are differentiated into dopaminergic neurons. Further, HFAs KD for β-catenin were also co-cultured with LUHMES neurons then exposed to HIVBaL. Microtubule-associated protein 2 (MAP2) expression was assessed for neuronal dendritic integrity at 72 hrs post-treatment of ACM or HFAs by western blot and immunofluorescence. ACM from HIV infected or β-catenin KD HFAs resulted in ≈

80% decrease in neuronal β-catenin expression with no effect on the housekeeping protein GAPDH. ACM from HIV infected or β-catenin KD HFAs also resulted in reduction of MAP2 expression by ≈ 50 and 80%, respectively, as measured by WB. Co-culturing β-catenin KD astrocytes with neurons and HIVBaL infection also led to a significant reduction in neuronal MAP2 expression by immunofluorescence. Taken together, HIV-mediated disruption of Wnt/β-catenin signaling in astrocytes lead to significant neuronal injury, highlighting the importance of Wnt/β-catenin signaling in astrocytes for astrocyte-neuronal communication and neuroprotection. This work is supported by F32 NS0889442-01 (VL) and 5R01 NS060632-06 (LA).

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Poster

760. Neuron-glia Interactions

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Topic: B.11. Glial Mechanisms

Support: Prof. KH René Koczorek Stiftung

Title: Identification of mineralocorticoid receptors as potential targets to modulate nociceptive neurons but not glia cells

Authors: ***S. A. MOUSA**[1], M. SHAQURA[1], X. LI[1], M. AL-MADOL[1], A. BEYER-KOCZOREK[2], S. MICHAEL[1];
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Abstract: From years back - in addition to the glucocorticoid receptor (GR) - the mineralocorticoid receptor (MR) has been reported to contribute to the relief of clinical symptoms in patients with inflammatory diseases (Mertin et al., 1972). More recently, there is some evidence that MR are expressed in neurons and/or glia cells and may modulate nociception (Dong et al., 2012). We investigated (by PCR, WB, IHC) in spinal cord, dorsal root ganglia, and peripheral nerve bundle of naïve Wistar rats the exact type of sensory neurons and glia cells that express MR. Upon intraplantar and intrathecal application of the MR agonist aldosterone with and without the antagonist spironolactone we examined alterations in mechanical thresholds by von Frey filament testing. Double immunofluorescence confocal microscopy revealed that MR colocalized with the sensory neuron marker calcitonin gene-related peptide (CGRP) in sensory

nerve terminals within the dorsal horn of the spinal cord, in dorsal root ganglia neurons, and in peripheral nerve terminals innervating skin epidermis. Importantly, MR were found to be expressed neither in satelitte cells nor in Schwann cells excluding the involvement of glia cells. Intraplantar as well as **i**ntrathecal injection of aldosterone resulted in a significant and dose-dependent reduction of mechanical thresholds consistent with previous reports about an increased excitability of sensory neurons. This effect could be abolished with the antagonist spironolactone. Taken together, we could identify MR predominantly in unmyelinated and thinly myelinated nociceptive fibres but neither in other sensory neurons nor in glia cells which - upon activation - leads to a lowering of mechanical thresholds. This suggests a crucial role of MR in the modulation of pain at the spinal and peripheral level of the nervous system. Supported by the Prof. KH René Koczorek Stiftung

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Poster

760. Neuron-glia Interactions

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Support: Welcome Trust

NIH IRTA

Title: The role of the pre-Bötzinger complex astrocytes in central respiratory CO2 chemosensitivity

Authors: *S. SHEIKHBAHAEI[1,2], N. MARINA[2], V. RAJANI[3], S. KASPAROV[4], G. D. FUNK[3], J. C. SMITH[1], A. V. GOURINE[2];
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Abstract: Current models of respiratory CO2 chemosensitivity are centered around a function of a defined group of pH-sensitive neurons residing in the medullary retrotrapezoid nucleus (RTN) (Guyenet, 2014), though significant prior evidence suggests that the functional respiratory

chemoreceptors are also located in other brainstem areas including the rhythm-generating region of the medullary pre-Bötzinger complex (preBötC). There is also evidence that brainstem astrocytes are highly sensitive to changes in PCO2/[H+] and play a role in the mechanisms of RTN chemosensitivity. In this study we investigated whether astrocytes intermingled with the preBötC circuits contribute to the respiratory response to CO2. To interfere with astroglial signalling by blocking vesicular release mechanisms, preBötC astrocytes were targeted to express light chain of tetanus toxin (TeLC), which cleaves certain SNARE proteins responsible for vesicular docking and fusion. In conscious rats, bilateral expression of TeLC in preBötC astrocytes was associated with a significant reduction of the ventilatory response to 10% inspired CO2 (by 22%; n=5, p=0.008). In comparison, inhibition of RTN neurons expressing DREADD(Gi) receptors bilaterally by application of clozapine-N-oxide (CNO, 2.5 mg/kg), reduced the ventilatory response to 10% inspired CO2 by 19% (n=5, p=0.002). In anesthetized and artificially-ventilated rats, hypercapnia-induced increases in phrenic nerve activity were reduced (by 30.3%; n=5, p=0.034) in rats transduced to express TeLC in preBötC astrocytes. These data suggest that the activity of respiratory rhythm-generating circuits of the preBötC are controlled by neighboring astrocytes, which constitute an important component of the brainstem mechanisms underlying the CO2 drive to breathe.

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Poster

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Support: Ministère Enseignement Supérieur et de la Recherche

Title: Aβ oligomers impacts astrocytic processes calcium excitability and structural plasticity nearby hippocampal synapses

Authors: A. BOSSON, S. BOISSEAU, A. BUISSON, *M. ALBRIEUX;
Grenoble Inst. des Neurosciences, Univ. Grenoble Alpes, Grenoble cedex 9, France

Abstract: Synaptic loss is thought to be one of the earliest events in Alzheimer's disease (AD). However, the key mechanisms that maintain synapse integrity or initiate synapse dysfunction in AD remain unknown. In early phase of AD, soluble amyloid β peptide (Aβ) is known to

selectively mediate impairment of synaptic plasticity and synaptic loss. Recent studies suggest that astrocytes contribute to morphological and functional changes observed during synaptic plasticity and play a major role in synaptic dysfunction. Our hypothesis is that Aβ acts directly on synaptic spine but also on its perisynaptic astrocytic partner emphasizing its impact on dendritic spine. In that context, we first studied the impact of oligomeric Aβ (Aβo) on astrocytes at both a functional and structural level. Combining confocal calcium imaging and electrophysiological experiments on mouse acute brain slices, we analyzed the impact of Aβo on calcium excitability in the hippocampal astrocytic network along with in single astrocyte focusing on astrocytic processes that are in close relationship with glutamatergic synapses. We showed that Aβo 100 nM for 5 min induced an increase of the proportion of active astrocytes in hippocampal stratum radiatum (28 % increase; $p < 0.05$) and an increase of the frequency of calcium signals within individual active astrocyte (56 % increase; $p < 0.05$). This leads to a global astrocytic hyperexcitability and excessive synchronization of the astrocytic network in hippocampal stratum radiatum. Concurrently, Aβo increased calcium excitability in astrocytic processes and modified the spatiotemporal dynamic of calcium signaling in these microdomains. A pharmacological approach allowed us to highlight some molecular actors involved in these compartmentalized calcium hyperexcitability within astrocytic processes. These functional impacts of Aβo on astrocyte excitability went along with structural remodeling of perisynaptic astrocyte processes. Thus, these results suggested that astrocytes are directly affected by Aβo exposure leading to both functional and structural consequences. Further work will be performed to monitor the repercussions of these astrocyte modifications on neighboring synaptic plasticity mechanisms such as long term potentiation. Identifying molecular actors involved in setting up plasticity impairments in both neuronal and astrocytic partners will allow us to decipher the beneficial and deleterious role of neuron-astrocyte interaction in AD synaptic impairments.

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Poster

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Title: Serial section electron microscopy of glia in adult neocortex

Authors: *D. R. BERGER, J. W. LICHTMAN;
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Abstract: Using the Automated Tape-collecting Ultra-Microtome technique followed by imaging in a Scanning Electron Microscope (ATUM-SEM), we acquired a three-dimensional volume of adult somatosensory mouse cortex (~50 x 50 x 60 μm) at ultra-high resolution (3 x 3 x 29 nm per pixel) [Kasthuri et al., 2015] and used this image data to explore all the glia in this volume. We found that the volume intersected with 7 glial cell somata and 26 neuronal somata. The glia were classified by their electron microscopy appearance as three microglia, two oligodendrocyte precursor cells (NG2-OPCs), one oligodendrocyte and one astrocyte. We reconstructed the complex arbors of these cells by manual painting using freely available segmentation software that we developed for this project (VAST Lite, http://software.rc.fas.harvard.edu/lichtman/vast/). We found that each one of these glial cell types interacted with the neuronal elements in a different way. For each microglial cell our data suggested that many 100s of its terminal processes end close to the tips of dendritic filopodia. Consistent with this finding, 28% (range 4.2% - 58.3% depending on dendrite) of dendritic filopodia ended next to microglial processes. This association with neuronal filopodia was true for spiny dendrites, aspiny dendrites, the relatively spine-free segments of spiny dendrites close to the cell body, and cell bodies of neurons themselves. Rarely, we observed debris within the microglial processes. In distinction to the dendritic associations of microglia, NG2-OPCs enveloped ends of axonal processes. We found one case in which an NG2-OPC process enveloped an axonal synaptic bouton and its associated dendritic spine. Moreover NG2-OPCs appeared to completely phagocytose folded pieces of axons (often with vesicles). Oligodendrocyte branches were easily distinguished from other glia because they generated myelin sheaths. The sheaths were exclusively at terminal branches of the oligodendrocytes. Interestingly, comparing two oligodendrocyte branches, one formed on average thicker myelin sheaths than the other (rank sum test, $p=0.014$). Astrocyte processes were ubiquitous in the volume branching out between neuronal processes, closely associating with inhibitory dendrites and sheathing about a third of the excitatory and inhibitory synapses. Astrocytes formed multilayered glomerular capsules at <1% of synapses. The determination of which synapses were encapsulated appeared to be based on the identity of the axon rather than the dendrite. These results suggest that serial electron microscopy can be helpful in determining the specific roles of the different glial cell types within cerebral cortex.

Disclosures: D.R. Berger: None. **J.W. Lichtman:** None.

Poster

760. Neuron-glia Interactions

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Title: Relevance of neuron-glia interactions to the action of oxytocin in pain processing

Authors: *J. WAHIS, B. BELLANGER, T. MADUNA, V. LELIÈVRE, P. POISBEAU, A. CHARLET;
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Abstract: Oxytocin (OT) is a hypothalamic hormone and neuropeptide well known for its numerous roles in social interaction, anxiety and pain modulation, among others. Particularly, OT can modulate the local circuitry of the central amygdala (CeA) in order to decrease the fear response. Here we study the action of OT on the calcium dynamics of astrocytes and the relevance of the astrocyte-neuron interaction to the OT neuromodulatory effect in the CeA. Through calcium imaging and patch clamp experiments on horizontal slices of rat amygdala, we characterize the response of astrocytes and neurons of the CeA upon specific activation of OT-receptor and study further the cellular mechanisms involved as well as possible astrocyte to neuron gliotransmission. Through a neuropathic pain model we tested the relevance of those mechanisms *in vivo*. Taken together, our results provide insight into the mechanisms underlying OT action in the CeA and its role in pain processing.

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Poster

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Support: Schram-Stiftung- 2011

Title: Activity dependent remodeling of ECM monitored by extracellular proteolysis of brevican

Authors: *J. B. SINGH[1,2], N. J. PANDYA[3], A. B. SMIT[3], K. W. LI[3], C. SEIDENBECHER[2], R. FRISCHKNECHT[2];
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Abstract: The chondroitin sulfate proteoglycan brevican is one of the main components of the mature extra cellular matrix (ECM). It is the smallest member of the family of lecticans. Together with other proteoglycans and glycoproteins such as tenascinR, the lecticans form a tight meshwork around neurons. It has been suggested that the ECM inhibits structural plasticity by stabilizing synaptic contacts and preventing synaptogenesis in the adult. On the other hand the ECM provides important instructive information necessary for LTP, a measure for synaptic plasticity. It has been shown that brevican and the other lecticans can undergo proteolytic cleavage, mainly by ADAMTS4 (a disintegrin and metalloprotease with thrombospondin motifs) and ADAMTS5. Here we hypothesise that proteolysis of the ECM is required to alter locally the structure of the ECM to allow for synaptic rearrangements in the adult in a restricted area and time. Interestingly, it has been reported that during the first minutes to hours after LTP induction neurons show enhanced structural plasticity. Therefore we wondered whether brevican as a representative of the ECM is particularly proteolytically cleaved during LTP. To this end we induced chemical LTP in acute hippocampal slices and performed quantitative western blotting to measure brevican cleavage, as well we as an unbiased approach by MS screening for modulation of ECM upon activity. We found a marked increase in brevican cleavage compared to control slices 15-60 min after LTP induction in both approaches. Cleavage was reduced to basal level and increase in brevican full length was observed, when a broad spectrum protease inhibitor as well specific protease inhibitors were used during the experiment. This indeed indicates that proteolytic cleavage and therefore remodelling of the ECM may be involved in learning and memory processes that require structural plasticity

Disclosures: J.B. Singh: None. **N.J. Pandya:** None. **A.B. Smit:** None. **K.W. Li:** None. **C. Seidenbecher:** None. **R. Frischknecht:** None.

Poster

760. Neuron-glia Interactions

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 760.20/B45

Topic: B.11. Glial Mechanisms

Support: RO1 NS081189

Title: Mir-133b inhibits glial scar formation and promotes brain remodeling after treatment of stroke in rats with multipotent mesenchymal stromal cells

Authors: *F. WANG;
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Abstract: Multipotent mesenchymal stromal cells (MSCs) improve functional recovery after stroke in rats, in-part by reducing glial scar formation and promoting neurite outgrowth. MicroRNA-133b (miR-133b) has been shown to participate in stroke recovery. We hypothesize that MSCs with enhanced miR-133b will further inhibit glial scar formation and promote neurite outgrowth. In this study, six male adult rats were subjected to middle cerebral artery occlusion (MCAo) and injected intravenously with MSCs transfected with miR-133b (Real-time PCR showed miR-133b level in these MSCs increased significantly compared to naive MSCs, 60.5±10.5 fold, $p<0.01$) or naïve MSCs, at 1 day after MCAo. The function of miR-133b enriched MSC group significantly improved neurological recovery from stroke compared to the naïve MSC group ($P<0.05$). Animals were sacrificed 28 days after stroke. MiR-133b enhanced MSC treatment reduced the thickness of the glial scar wall, indicated by Vimentin staining (pixel relative thickness: miR-133b 61.16±14.22, naïve MSC 83.90±6.41; $P<0.01$). Connective tissue growth factor (CTGF) and Ras homolog gene family, member A (RhoA) are targets of miR-133b. Both CTGF and RhoA inhibit neurite outgrowth. Immunostaining showed a decreased expression of CTGF in reactive astrocytes in the scar boundary zone in the miR-133b enhanced MSC treated rats compared to the naive treated rats (positive staining area: miR-133b 0.11±0.07 %, naïve MSC 0.26±0.14%; $P<0.05$). The expression of RhoA, likewise, decreased in the miR-133b enhanced MSC treated rats (positive staining area: miR-133b 0.12±0.09%, naïve MSC 0.27±0.15%; $P<0.05$). MiR-133b regulation of neurite outgrowth via ERK1 and PI3K/Akt signaling pathway by RhoA suppression was further demonstrated by Western-blot. *In vitro*, cultured primary astrocytes were subjected to oxygen and glucose deprivation (OGD). MSCs enriched with miR-133b were co-cultured with astrocytes subjected to OGD for 24 hours. Real-time PCR showed miR-133b level was significantly increased in miR-133b treatment group compared with naïve MSC treatment group (by 4.35±0.56 fold, $p<0.05$). Correspondingly, the expression of CTGF in the miR-133b treated astrocytes significantly decreased compared to MSC group. Our data suggest that enhanced miR-133b reduces CTGF expression and thereby reduces the glial scar formation. In addition, increased miR-133b level in brain is related to reduction of RhoA expression via the ERK1 and PI3K/Akt signaling pathway, and promotes the

neurite outgrowth. Thus MSCs enriched with miR-133b by reduction of CTGF and RhoA likely contribute to improved functional recovery after stroke.

Disclosures: F. Wang: None.

Poster

760. Neuron-glia Interactions

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 760.21/B46

Topic: B.11. Glial Mechanisms

Support: NIAAA 5R01AA018799

Title: Akap200 scaffolding protein controls blood-brain barrier responses to alcohol

Authors: *S. PARKHURST[1], A. LEGENDRE[1], E. KONG[2], F. W. WOLF[2,1];
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Abstract: Alcohol is the most commonly abused drug today, yet our knowledge of its biological mechanisms and our ability to effectively treat alcoholism is lacking. The fruit fly *Drosophila* is a model for the molecular and behavioral actions of alcohol, including the development of tolerance to its sedating effects. The fly blood-brain barrier (BBB) provides a physical and chemical protection for the brain, and is composed of the perineurial glia (PG) and the subperineurial glia (SPG). The protein kinase A scaffolding protein, Akap200, increases expression following exposure to alcohol. Decreased Akap200 expression in the whole fly, in all glia, and specifically in the PG resulted in a decreased ability to develop alcohol tolerance. Acute alcohol exposure caused morphological rearrangement of the PG that was delayed when Akap200 expression was reduced in the PG; the chemical and physical BBB functions were unaffected. Ca2+/CaM signaling, that may regulate Akap200 function, was critical for BBB-dependent alcohol tolerance. Our findings implicate the glial BBB in the development of behavioral plasticity, and suggest that the barrier communicates with central brain neurons to facilitate the development of alcohol tolerance.

Disclosures: S. Parkhurst: None. **A. Legendre:** None. **E. Kong:** None. **F.W. Wolf:** None.

Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.01/B47

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH: AG037481

NIH: AG037919

NIH: ES024233

NIH: ES021243

NIH: K01AG044490

DOD: W81XWH-13-1-0384

Title: Genome-wide approaches reveal Bexarotene controlled regulatory networks in APOE3 mice

Authors: *K. NAM[1], A. MOUNIER[1], J. SCHUG[2,3], N. F. FITZ[1], I. LEFTEROV[1], R. KOLDAMOVA[1];
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Abstract: Nuclear receptors Retinoid X receptors (RXRs) are ligand-activated transcription factors that heterodimerize with other nuclear receptors to generate functional transcription factors. Previous studies showed that RXR synthetic and highly selective agonist Bexarotene improves memory in mice expressing human apolipoprotein E (APOE) - isoforms APOE3 and APOE4. Our preliminary studies demonstrate also that Bexarotene increases neuronal differentiation and adult neurogenesis in APOE4 mice (not published). To identify direct RXR targets genome-wide in APOE3 mice we applied chromatin immunoprecipitation for transcription factor binding followed by high-throughput sequencing (ChIP-seq). We demonstrate that Bexarotene treatment induced changes in the distribution of RXR binding - there was a significant shift towards RXR binding in promoter regions of annotated genes in Bexarotene treated, compared to control mice (0.4% vs 10%); second, functional annotation clustering using DAVID and IPA web tools revealed that GO categories chromatin modification and chromatin organization were significantly enriched only in Bexarotene treated APOE3 mice. Thus highly and significantly enriched clusters were transcription factor activity, axonal

guidance and neuritogenesis. As a next step, to determine how Bexarotene affects mRNA levels, and potentially gene expression in brain, we applied high-throughput mRNA-seq with RNA isolated from cortices of the same mice: IPA analysis of RNA-seq datasets showed that differentially affected categories are: learning, cognition, behavior, synaptic transmission, axon- and neurites outgrowth. Several signaling pathways important for axonal guidance and neuritogenesis were identified as significantly overlapping in ChIP-seq and RNA-seq datasets, such as Wnt/β-catenin, PI3K/AKT and CREB signaling. These data were further validated in cell culture and *in vivo* using QPCR and morphological analysis of Bexarotene promoted neuritogenesis. The results of this study suggest that Bexarotene can affect memory function through regulation of several, amongst them Wnt/β-catenin and PI3K/AKT signaling pathways involved in neuritogenesis.

Disclosures: K. Nam: None. **A. Mounier:** None. **J. Schug:** None. **N.F. Fitz:** None. **I. Lefterov:** None. **R. Koldamova:** None.

Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.02/B48

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: VA Merit 1I01BX001067-01

Alzheimer’s Association NPSPAD-1l-202149

NIH P30 AG035982

Title: GRK5 deficiency renders vulnerability to cognitive deficits triggered by mild intermittent hypoxia

Authors: *W. Z. SUO[1,2,3], P. SINGH[1], W. PENG[1], Q. ZHANG[1], X. DING[1];
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Abstract: Obstructive sleep apnea (OSA) leads to sleep fragmentation and intermittent hypoxia (IH). The latter posts significantly increased health risks for cardiovascular system. In addition, recent evidence indicates that OSA may also increase the risk of suffering from cognitive impairment such as Alzheimer’s disease (AD), though the underlying mechanisms remain elusive. In parallel, our recent studies have suggested that G protein-coupled receptor kinase-5

(GRK5) deficiency accelerates AD pathogenesis most likely by selectively rendering cholinergic neurons more vulnerable to various degenerative insults, including hypoxia. To test this hypothesis, we placed young (4 months) wild type (WT) and GRK5 knockout (KO) mice in the absence and presence of mild IH (8%/21% O2 90 sec cycle for 8 hours a day) for a month. After completion of the IH treatment, the mice were transferred to behavioral room and environmentally adapted for two weeks before they were behaviorally assessed with a battery of tasks. Our results showed that the mild IH only induced marginally abnormal behavior (slightly elevated anxiety with most others unchanged) in WT mice but in the KO mice it caused significantly more behavioral deficits, ranging from weakened balancing function, elevated anxiety, slowed swimming speed, reduced spontaneous alternation score in Y maze, and worsened performances in Morris water maze and radial arm water maze that measure spatial memory. Although the pathological analyses are pending, these behavioral results support our hypothesis and suggest that GRK5 deficiency makes the mice more vulnerable to wide range of behavioral impairments, including spatial memory deficits.

Disclosures: W.Z. Suo: None. **P. Singh:** None. **W. Peng:** None. **Q. Zhang:** None. **X. Ding:** None.

Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

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Program#/Poster#: 761.03/B49

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: : QREN (Quadro de Referência Estratégico Nacional 2007-2013) project “DoIT - Desenvolvimento e Operacionalização da Investigação de Translação”

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“Fundação para a Ciência e a Tecnologia” (FCT), project references: PEst-C/SAU/LA0001/2013-2014, and post-doctoral fellowship SFRH/BPD/86551/2012.

Title: Impairment in hippocampal newly-generated neurons maturation and exacerbation of memory loss in a diabetic-like Alzheimer’s disease mouse model

Authors: *E. B. FERREIRO[1,2,3], M. LANZILLO[1,3], A. M. CARVALHO DA SILVA[1,2,3], G. MASTRELLA[1,3], S. MOTA[1,2,3], A. R. FONTES[1,3], I. L. FERREIRA[1,2,3], C. R. OLIVEIRA[1,2,3], J. VALERO[1,2,3], A. C. REGO[1,2,4,3];

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Abstract: Type 2 diabetes mellitus, a pathology associated with increased blood glucose levels (hyperglycemia), has been linked to Alzheimer's disease (AD). Indeed, hyperglycemia, oxidative stress, and dysfunctional insulin signaling are common features of these two age-related diseases. Therefore, elucidate the molecular mechanisms underlying the neurodegenerative process that occurs in AD under hyperglycemia is of utmost relevance. Moreover, little is known about how the perturbation of glucose metabolism affects the formation of new neurons during adult hippocampal neurogenesis, a process that plays an important role in learning and memory. In order to evaluate whether hyperglycemia aggravates the alterations of hippocampal adult neurogenesis in AD and further impair memory, 2 month-old triple transgenic AD (3xTg-AD) mice were treated with an elevated dose of sucrose over 6 months. Non transgenic (NonTg) and 3xTg-AD mice treated with sucrose presented decreased glucose tolerance and increased levels of glycated hemoglobin, cholesterol and leptin, in comparison with the respective non-treated group. Untreated 3xTg-AD mice exhibited increased glucose tolerance, when compared to NonTg, which was associated to increased insulin levels. Interestingly, hyperglycemia had a negative effect on learning and spatial memory of 3xTg-AD mice, leading to the impairment of these cognitive functions. Furthermore, our results show that hyperglycemia potentiated cell proliferation in the subgranular zone of the dentate gyrus of the hippocampus, namely of neuroblasts, which in the case of sucrose-treated 3xTg-AD mice did not contribute to an increase in the total number of neuroblasts or immature neurons. In these mice, we also observed decreased dendrite complexity of immature neurons, when compared to untreated 3xTg-AD mice. These data suggest that hyperglycemia enhances AD pathology, contributing for the impairment in neurogenesis, defective learning and memory loss.

Disclosures: E.B. Ferreiro: None. **M. Lanzillo:** None. **A.M. Carvalho da Silva:** None. **G. Mastrella:** None. **S. Mota:** None. **A.R. Fontes:** None. **I.L. Ferreira:** None. **C.R. Oliveira:** None. **J. Valero:** None. **A.C. Rego:** None.

Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.04/B50

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: DGAPA PAPIIT IN209413

CONACyT 155242

Departamento de Ciencias de la Salud, UAM-Lerma

División de Ciencias Biológicas y de la Salud, UAM-Lerma

Doctorado en Ciencias Biológicas, UAM-Xochimilco

Title: High-fat and high-fructose diet intake differentially affects cognitive performance in male and female 3xTg-AD mice

Authors: *K. R. GUZMAN-RAMOS[1], L. X. AYALA-GUERRERO[2], F. BERMÚDEZ-RATTONI[2], P. GARCÍA-DELATORRE[3], G. PACHECO-LÓPEZ[1];
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Abstract: It is known that high caloric diets and type 2 diabetes are risk factors for the development of dementias, particularly Alzheimer's Disease (AD). Even though AD has a high prevalence among elderly women over men, there is no clear hormonal, metabolic of physiological factor to explain such prevalence. In order to study the effects of a high caloric diet on the development of AD and how it affects males and females we exposed a murine model of AD harboring three mutations related to the amyloid beta and p-tau accumulation (3xTg-AD) to a high-fat (60% calories from fat) plus high-fructose (20% in tap water) diet (HFHF). Additionally we exposed non-transgenic mice to the same HFHF diet and after 30 days assessed the cognitive performance in object recognition and Morris water maze tasks. As a consequence of HFHF diet exposure, only 3xTg-AD male mice showed cognitive deficits as well as metabolic dysfunctions reflected on poor glucose tolerance and higher adiposity. These data suggest that an early exposure to high caloric food has a powerful impact on the acceleration or production of cognitive impairments in the 3xTg-AD male mice, indicating the possibility of a protective factor in young female 3xTg-AD.

Disclosures: K.R. Guzman-Ramos: None. **L.X. Ayala-Guerrero:** None. **F. Bermúdez-Rattoni:** None. **P. García-delaTorre:** None. **G. Pacheco-López:** None.

Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.05/B51

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Title: A novel administration of systemic streptozotocin leads to alterations relevant to vascular dementia and Alzheimer's disease

Authors: *A. S. MURTISHAW[1], C. F. HEANEY[2], M. M. BOLTON[2], K. D. BELMONTE[2], M. A. LANGHARDT[2], J. W. KINNEY[2];
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Abstract: Diabetes Mellitus (DM) has been identified as a major risk factor for developing vascular dementia (VaD) and Alzheimer's disease (AD). Among the various characteristics associated with DM, disruptions to insulin signaling have been implicated as the main factor that confers the greatest risk for these dementia-related diseases. Streptozotocin (STZ), a compound that targets and destroys insulin producing pancreatic β-cells, has been utilized to better understand DM. Additionally, the administration of STZ has been used to model sporadic AD due to its ability to alter behavior and hyperphosphorylate tau in the brain. Studies utilizing STZ often rely on a very high single dose or repeated doses of a slightly lower dose, both of which are often associated with increased mortality and renders sick animals not optimal for behavioral testing. We optimized a multiple low-dose STZ schedule, administered over the course of 15 days that led to significantly elevated blood-glucose levels and overall healthy animals following a battery of standardized behavioral tests. Starting the sixth week after the first STZ injection, animals were assessed in the open field and Novel object recognition tasks. Brains were removed and prepared for either western blotting to investigate proteins related to tau pathology and insulin signaling, specifically insulin degrading enzyme, or for immunohistochemistry to evaluate microglia activity, amyloid plaque deposition, and microinfarcts. Results indicate that our novel dosing schedule of STZ results in a viable and sustainable diabetic state and ultimately leads to alterations in learning tasks and dementia-related protein changes, with relevance to VaD, in particular that peripheral insulin disruption leads to wide-spread microglia activation throughout the brain.

Disclosures: A.S. Murtishaw: None. **C.F. Heaney:** None. **M.M. Bolton:** None. **K.D. Belmonte:** None. **M.A. Langhardt:** None. **J.W. Kinney:** None.

Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.06/B52

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Fundacion Alfonso Martin Escudero, Madrid Spain

Title: Sensorimotor Integration measured by a Reaching task in Neurodegenerative disease

Authors: ***M. A. SANTOS**[1], J. O'DOHERTY[2], G. RABINOVICI[1], B. L. MILLER[1], M. GORNO TEMPINI[1], P. SABES[2];
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Abstract: Background: Sensory-motor integration refers to the integration of visual and tactile/proprioceptive sensory information for the purpose of action planning and execution. Neurodegenerative disease syndromes cause prominent deficits of sensorimotor function, yet there is limited data characterizing these deficits and its underlying mechanisms are poorly understood. While various reaching studies involving large cohorts of stroke patients have been published, similarly-sized studies in patients with neurodegenerative disease are lacking. We report the largest reaching study in patients with neurodegenerative disease to date. Objective: To characterize sensorimotor integration ability in various forms of neurodegenerative disease with the overall goal of improving clinical diagnosis. Methods: More than 60 subjects diagnosed with various neurodegenerative conditions including early onset Alzheimer's disease (EOAD), posterior cortical atrophy (PCA), cortical basal syndrome (CBS), progressive supranuclear palsy (PSP), non-fluent, logopenic, and semantic variant forms of primary progressive aphasia (nfvPPA, lvPPA, svPPA), and behavioral variant frontotemporal dementia performed a reaching task and a limb proprioception task designed to measure various aspects of sensorimotor integration. Performance was correlated with neuroimaging data using voxel based morphometry. Results: Different diagnostic groups presented partially differentiable sensory-motor integration profiles. All patient groups were different from controls in at least one measure. Overall, patients with diagnoses associated to parietal and posterior temporal atrophy such as CBS, PCA, and lvPPA showed more problems in measures that reflect sensory-motor integration for planning such as initial reaching angle. Subjects with diagnoses associated to motor and premotor cortex atrophy such as CBS, PSP, and nfvPPA generally performed worse on measures of speed reflecting motor execution. Conclusion: These results demonstrate we can detect and measure sensory-motor integration deficits in patients and that we can capture distinctive profiles across different neurodegenerative disease syndromes which may be useful for improving clinical diagnosis.

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Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.07/B53

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: This research was supported by a grant from the Korea Research Institute of Bioscience and Biotechnology (KRIBB) Research Initiative Program (KGM4611512)

Title: Global gene expression in chemical-induced animal model for cognitive disorder

Authors: *H. LEE[1], S. CHOI[1], S.-R. LEE[2], S.-H. CHA[3], K.-T. CHANG[2], S. KIM[4]; [1]Chung-Ang Univ. Col. of Med., Seoul-City, Korea, Republic of; [2]Natl. Primate Res. Ctr., Korea Res. Inst. of Biosci. and Biotech., Cheongju, Korea, Republic of; [3]Dept. of Radiology, Chungbuk Natl. Univ. Col. of Med., Cheongju, Korea, Republic of; [4]Div. of Neurology, Dept. of Med., UBC Hospital, Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Alzheimer’s disease (AD) is a neurodegenerative disorder which observed amyloid plaques and neurofibrillary tangles. Appropriated medicine is not available so far. There are many animal models to imitate AD using mutant genes of presenilin and APP. However, these animal models which used mutant genes are based to familial dementia to developed young age. We proposed new animal model for AD using ibotenic acid (Ibo) and amyloid beta (Aβ) to induce neuronal cell loss. We injected ibotenic acid and Aβ into bilateral hippocampus of mouse at 6 week age. Animal behavioral test and histological analysis were shown to decline of learning, memory, neuronal cell loss and deposits of amyloid plaque in hippocampus regions. Total RNAs were used for global gene network. These results suggested that new animal model may be a useful tool to study as AD-like disease.

Disclosures: **H. Lee:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); This research was supported by a grant from the Korea Research Institute of Bioscience and Biotechnology (KRIBB) Research Initiative Program (KGM4611512). **S. Choi:** None. **S. Lee:** None. **S. Cha:** None. **K. Chang:** None. **S. Kim:** None.

Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.08/B54

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: The Weston Brain Institute

CIHR

Title: Using automated touchscreen system to evaluate attention deficits in mouse models of Alzheimer's disease: improving the transition from bench to bedside

Authors: *F. H. BERALDO[1], T. S. MASOOD[1,2], D. PALMER[5], D. I. WASSERMAN[5], S. D. CREIGHTON[5], M. F. COWAN[1], B. KOLISNYK[1,2], T. GEE[6], S. LIANG[6], R. BARTHA[1,3], S. C. STROTHER[6,7], V. F. PRADO[1,4], B. D. WINTERS[5], M. A. M. PRADO[1,4];
[1]Robarts Res. Inst., [2]Neurosci., [3]Dept. of Med. Biophysics, [4]Physiol. and Pharmacology/Anatomy and Cell Biol., Univ. of Western Ontario, London, ON, Canada; [5]Dept. of Psychology and Neurosci. Program, Univ. of Guelph, Guelph, ON, Canada; [6]Rotman Res. Institute, Baycrest Hosp., Toronto, ON, Canada; [7]Dept. of Med. Biophysics, Univ. of Toronto, Toronto, ON, Canada

Abstract: Classical behavioural tasks used to test cognition in mouse models are usually low throughput and are in general very distinct from human cognitive tests. A source of variability for testing drugs in animal models of disease is the lack of automation, reproducibility and influence by experimenters in behavioural testing. The Bussey-Saksida touchscreen tasks provide a new paradigm for testing cognitive deficits in animal models of dementia and addresses most of the pitfalls above. In this study, using the 5-Choice Serial Reaction Time Task (5-CSRTT) we compared the performance of two different mouse models of familial Alzheimer's Disease (AD) (5xFAD and 3xTG-AD) and a cholinergic deficient mouse model. The AD mice present mutations driving Aβ42 overproduction and accumulation of amyloid-β-plaques. In addition the 3xTG-AD mice present mutated tau. Both male and female AD mice were tested longitudinally at 4, 7 and 10 months of age. We tested reproducibility of the tests by performing the same experiments at both the University of Western Ontario and the University of Guelph. The data was then used to create an online database of mouse performance in cognitive tests. Cholinergic-deficient mice presented attention deficits at 4 months as previously published. In both sites we observed similar attention performance in the two AD mouse lines when probed in the 5-CSRTT therefore data were pooled. Both 5xFAD males and females showed attention deficits at 7 months of age when compared to their age matched controls. Male and female 3xTG-AD mice showed deficits in attention earlier at 4.5 months of age. The 3xTG-AD mice continued to show greater attention deficits, compared to wild-type controls, at 7 and 10 months of age (170 mice in total). 5xFAD mice present higher accumulation of amyloid than the 3xTG-AD line in earlier ages, suggesting that the Tau mutation, rather than the accumulation of amyloid, may interfere with attentional performance at 4 months. This work provides an initial screening of comparative cognitive deficits in distinct mouse models of AD showing

reproducibility and robustness of results. These automated tasks lend themselves to high-throughput, and during this project we have been able to test close to 300 mice per day. These results point to the potential usefulness of the touchscreen behavioural tasks as powerful tools for drug screening in AD and other neurodegenerative diseases.

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Poster

761. Alzheimer's Neurodegeneration: Animal Models

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Topic: C.02. Alzheimer's Disease and Other Dementias

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NCET (12-0055, 12-0065)

Fundamental Research Funds for the Central Universities (2014kJJCA07)

Title: The left fusiform gyrus is the crucial region of the neuroanatomical network underlying the core behavioral profile of semantic dementia

Authors: ***J. DING**[1], K. CHEN[3], Y. CHEN[2], Y. FANG[2], Q. YANG[3], Y. LV[4], N. LIN[5], Y. BI[2], Q. GUO[3], Z. HAN[2];
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Abstract: Semantic dementia (SD) is a progressive cerebral atrophy disorder characterized by the loss of semantic memory in both the verbal and nonverbal domains. Given that abnormal regions or tracts are co-atrophied in SD, little is precisely understood about the regions or tracts

actually causing such semantic deficits (SD-causing regions or tracts). To address these issues, the present study investigated the relationship between the degree of cortical atrophy [i.e., the gray matter volume (GMV)] or whiter matter atrophy [i.e., mean fractional anisotropy (FA) value] and the severity of semantic deficits (i.e., the performance on three tasks: oral picture naming, picture associative matching, and word associative matching) in 19 SD individuals. We found 36 atrophic regions in the patients, and these regions primarily involved the bilateral temporal, ventral frontal, and insular cortices. Three of the atrophied regions (left fusiform gyrus, left hippocampus, and left parahippocampal gyrus) were associated with semantic impairments related to SD, and the GMVs of these regions significantly correlated to the scores on each semantic task. The left fusiform gyrus was further determined as an SD-causing region, and its GMV significantly correlated to the semantic performance scores after partialling out the GMVs of the left hippocampus and the left parahippocampal gyrus. The association of the left fusiform gyrus with semantic disruptions in SD was well sustained even when we controlled for a range of potential confounding factors (total GMV, overall cognitive state, laterality of brain damage, and non-semantic task performance). Finally, we observed that the mean FA values of the white matter tracts connecting the left fusiform gyrus with the left hippocampus and the left inferior occipital gyrus significantly correlated to the severity of semantic impairment in SD patients, when controlling for the above potential confounding factors. These results reveal the causal structural network of the left FFG as the center of semantic impairments in SD, providing direct evidence for a part of the anatomical framework of the semantic network.

Disclosures: J. Ding: None. **K. Chen:** None. **Y. Chen:** None. **Y. Fang:** None. **Q. Yang:** None. **Y. Lv:** None. **N. Lin:** None. **Y. Bi:** None. **Q. Guo:** None. **Z. Han:** None.

Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.10/B56

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: France Alzheimer

FRM

ANR CoreAlz

Title: Alterations of learning-induced hippocampal ripples in a mouse model of Alzheimer’s disease impairs spatial memory formation

Authors: *O. NICOLE[1], S. HADZIBEGOVIC[1], J. GAJDA[2], B. BONTEMPI, PhD[1], T. BEM[2], P. MEYRAND[1];
[1]CNRS, Univ. Bordeaux, UMR-CNRS5293, Bordeaux, France; [2]Polish academy of science, Nalecz Inst. of Biocybernetics and biomedical engineering, Warsaw, Poland

Abstract: Post-learning hippocampal sharp wave-ripples (SWRs) generated during sleep or rest periods are thought to play a crucial role in information processing and memory formation. Accordingly, disrupting SWRs experimentally impairs spatial learning (Girardeau et al., Nat Neurosci 12(10): 1222-1223). While in pathological conditions, such as Alzheimer's disease (AD), abnormal hippocampal oscillations have been reported, the functional contribution of SWRs to the typically observed spatial memory impairments remains poorly understood. These memory impairments have been related to degenerative synaptic changes produced by the presence of soluble amyloid beta oligomers (Aβos) which, surprisingly, seem to spare the SWR dynamics during routine behavior. To unravel a potential effect of Aβos on SWRs in cognitively-challenged animals, we submitted vehicle- and Aβo-injected mice to spatial recognition memory testing in a modified version of the Y-maze tailored to maximizing spatial cognitive demand. After confirming the hippocampal-dependency of this task, we established its ability to detect spatial memory impairments, 15 days after a single intracerebroventricular injection of Aβos. We examined recognition memory performance either 10 minutes or 4 hours after encoding. While capable of forming short-term recognition memory, Aβ mice exhibited faster forgetting, suggesting successful encoding but an inability to adequately stabilize and retrieve previously acquired information. We then determined the signature of this Aβo treatment on hippocampal SWRs in mice without cognitive requirements or while undergoing a single spatial discrimination session. Without prior cognitive requirements, similar properties of SWRs (baseline occurrence rate, frequency, duration and power) occurring during slow wave sleep periods were observed in Aβ and control mice. In contrast, when cognitively challenged, the post-encoding and -recognition peaks in SWR occurrence rates observed in the first 40 min of recording in controls were abolished in Aβ mice, indicating impaired hippocampal processing of spatial information. Thus, our results reveal the crucial involvement of SWRs in spatial memory formation and identify the Aβ-induced impairment in SWRs dynamics as a putative disruptive mechanism responsible for the spatial memory deficits associated with AD.

Disclosures: O. Nicole: None. **S. Hadzibegovic:** None. **J. Gajda:** None. **B. Bontempi:** None. **T. Bem:** None. **P. Meyrand:** None.

Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.11/B57

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Novel 5-HT6 antagonist, SUVN-502 potentiates the effects of Donepezil on neurochemical and electrophysiological activity in rat hippocampus

Authors: S. DARIPELLI, G. BHYRAPUNENI, *K. MUDIGONDA, V. BENADE, G. AYYANKI, V. KAMUJU, R. PONNAMANENI, A. MANOHARAN, R. NIROGI;
Suven Life Sci., Hyderabad, India

Abstract: SUVN-502 is a potent and selective 5-HT6 antagonist being developed for the symptomatic treatment of Alzheimer's disease. SUVN-502 is orally bioavailable and has adequate brain penetration. SUVN-502 exhibited pro-cognitive properties when tested in various rodent models. When administered alone, SUVN-502 increased acetylcholine levels in brain regions involved in learning and memory, providing the neurochemical basis for the pro-cognitive effects in rodent models. Effect of SUVN-502 in combination with donepezil was evaluated using brain microdialysis for the modulation of acetylcholine, and EEG for the effects on power density of stimulation induced theta in hippocampus. Effect on the hippocampal acetylcholine was tested with SUVN-502 (3 mg/kg, p.o.) administered alone and in combination with donepezil (1 mg/kg, s.c.). Effect on the hippocampal theta activity was tested after administration of SUVN-502 (1 mg/kg, i.v.) along with donepezil (0.3 mg/kg, i.v.). Hippocampal theta activity was elicited by electrical stimulation of Nucleus Pontis Oralis in urethane anesthetized male Wistar rats. SUVN-502 alone produced moderate increase in acetylcholine levels. However, in combination with donepezil, SUVN-502 produced significant increase in hippocampal acetylcholine levels compared to donepezil alone. SUVN-502 produced significant potentiation of the donepezil evoked theta power in hippocampus. These results provide the neurochemical and neurophysiological evidence that SUVN-502 in combination with acetylcholinesterase inhibitor may be beneficial in the treatment of cognitive deficits associated with Alzheimer's disease.

Disclosures: **S. Daripelli:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **G. Bhyrapuneni:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **K. Mudigonda:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **V. Benade:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **G. Ayyanki:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **V. Kamuju:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **R. Ponnamaneni:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **A. Manoharan:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD.

Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.12/B58

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Korea Institute of Oriental Medicine Grant K15310

Title: Alleviating effects of Fructus mume extracts on cognitive impairments in 5XFAD transgenic mice

Authors: *J.-C. PARK[1], J. MA[1], W. JEON[2], J.-S. HAN[1];
[1]Konkuk Univ., Seoul, Korea, Republic of; [2]Korea Inst. of Oriental Med., Daejeon, Korea, Republic of

Abstract: Previous studies have demonstrated that Fructus mume (F. mume) extracts alleviated cognitive deficit in rats with chronic cerebral hypoperfusion and mice with scopolamine treatments. The present experiment was conducted to examine the effects of F. mume on cognitive impairments in the animal model for Alzheimer's disease (AD), 5XFAD transgenic mice with five familial AD mutations. The 5XFAD animal model is known to exclusively generate amyloid beta-42 and exhibit cognitive impairments. Daily administration of F. mume was started at 3 months of age and continued for 90 days. Cognitive function was evaluated in spatial memory version of Morris water maze task, object/location novelty recognition test, and contextual fear conditioning at the age of 6 months. In the behavioral tasks, 5XFAD mice with vehicle treatment showed impairments of hippocampus-dependent memory compared with those of non-Tg littermates, which was reversed by treating F. mume to 5XFAD mice. To elucidate the possible mechanisms underlying this memory improving effects of F. mume on 5XFAD mice, we examined alterations in hippocampal cholinergic function. As a result, reduced hippocampal choline acetyltransferase (ChAT) levels in 5XFAD mice were reversed by F. mume treatment, indicating that F. mume has enhancing effects on cholinergic neuronal functions. These results suggest that F. mume might have therapeutic effects on cognitive impairments in AD. Supported by a grant (K15310) from the Korea Institute of Oriental Medicine (KIOM).

Disclosures: **J. Park:** None. **J. Ma:** None. **W. Jeon:** None. **J. Han:** None.

Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.13/B59

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Canadian Institutes of Health Research MOP102532

Title: Neuropathological correlates of cognitive impairments in Alzheimer's disease

Authors: *F. CALON[1], C. TREMBLAY[1], A. FRANÇOIS[1], M. VANDAL[1], D. BENNETT[2]; [1]Fac Pharm. and CRCHUQ, Laval Univ., Quebec, QC, Canada; [2]Rush Alzheimer's Dis. Ctr., Chicago, IL

Abstract: The association between cognitive symptoms and post mortem neuropathological markers remain poorly defined in mild cognitive impairment (MCI) and Alzheimer's disease (AD). We therefore investigated the relationship between *ante mortem* global cognitive scores and series of key AD neuropathological markers assessed *post mortem* in the same brain cortex region from the same 36 volunteers (12 NCI, 12 MCI and 12 AD) from the Religious Order Study. Homogenates from the anterior parietal cortex were subjected to differential centrifugation procedures to generate soluble, detergent-soluble, insoluble formic acid and insoluble sarkosyl fractions. Biochemical approaches (Western immunoblots and ELISA) were performed to determine the relative levels of tau, Aβ, synaptic proteins and other AD-relevant markers. Semi-quantitive assessments of Aβ plaques, tau-laden tangles and TDP-43 inclusions were also analyzed. Overall, the strongest negative correlation coefficients were obtained for insoluble phosphorylated tau, insoluble Aβ42 and neurofibrillary tangles counts. Strong inverse associations were also established for TDP-43-positive cytoplasmic inclusion, total insoluble tau and Aβ plaque counts. The analysis of insoluble tau extracted using formic acid or sarkosyl-based procedures led to similar results. Of note, synaptophysin and septin were the two synaptic proteins positively associated with cognitive scores. No correlation was detected with soluble Aβ42 or soluble tau. In conclusion, our data collectively highlight the importance of the association between cognitive decline and the accumulation of phosphorylated tau and Aβ42 into a detergent-insoluble form. This substantiates the relevance of investigating these markers to understand the pathogenesis of AD and develop therapeutic tools.

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Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.14/B60

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Impaired hippocampal synapse remodeling on GABAergic neurons correlates with memory deficits

Authors: *L. C. SCHMID, M. MITTAG, S. POLL, J. STEFFEN, S. REMY, M. FUHRMANN; DZNE, Bonn, Germany

Abstract: Aberrant neuronal activity and disturbed network function are important factors associated with Alzheimer's disease. Altered connectivity of inhibitory interneurons to excitatory neurons may contribute to the imbalance between excitation and inhibition and thereby destabilize the network. To analyze the effect of Aβ on network connectivity we investigated the structural plasticity of OLM interneurons in the hippocampus. OLM interneurons receive excitatory input in the stratum oriens and send axonal projections to the stratum lacunosum-moleculare where they synapse onto the distal dendrites of CA1 pyramidal neurons. Here, we analyze for the first time the structural plasticity of dendritic spines and axonal boutons of OLM interneuons in the stratum oriens and stratum lacunosum-moleculare respectively by long-term two-photon *in vivo* imaging over a period of 7 month. Dendritic spine density [0.7 +/- 0.05 μm^{-1}] was similar to that previously reported for interneurons in the cortex and significantly increased during aging while axonal bouton density [0.3 +/- 0.05 μm^{-1}] in the stratum lacunosum-moleculare stayed stable with increasing age. Throughout disease progression of APP transgenic mice (APP_{swe}/PS1dE9) dendritic spine turnover was significantly increased while the density stayed stable. Additionally, we observed a distinct loss of axonal structures. Our findings indicate that the connectivity of OLM interneurons is impaired during amyloidogenesis and might affect their role in hippocampal circuit. To further evaluate if altered spine dynamics could be relevant for learning deficits in APP transgenic mice, we analyzed the structural plasticity of spines during an associative learning task. In wild-type mice we observed an increase in gained spines during the learning phase, which were subsequently stabilized while the spine gain was absent in APP transgenic animals. This indicates that altered synaptic plasticity of dendritic spines might contribute to the learning deficit in APP transgenic mice.

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Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.15/B61

Topic: F.01. Human Cognition and Behavior

Support: Heart and Stroke Foundation of Canada 13-0001867

Brenda Strafford Foundation Chair in Alzheimer Research

Alberta Innovates-Health Solutions Health Senior Scholar Award

University of Calgary Seed Grant Award

Canadian Institutes of Health Research

Alberta Innovates-Health Solutions Postdoctoral Fellowship Award

Title: Lifetime and current physical and cognitive activity: Impact on current cognitive performance

Authors: *L. L. DROGOS[1,2], G. ESKES[14], R. LONGMAN[3,4,5], S. GILL[2,6], A. TYNDALL[1,2], M. H. DAVENPORT[1,2], C. M. FRIEDENREICH[7,8,9], D. B. HOGAN[7,7,3,10], M. D. HILL[11,7,3], B. J. WILSON[10], M. J. POULIN[1,2,3,12,13];
[1]Pharmacol. & Physiol., [2]Hotchkiss Brain Inst., [3]Clin. Neurosciences, [4]Psychology, [5]Rehabil. Psychology, [6]Med. Sci., [7]Community Hlth. Sci., [8]Oncology, [9]Cancer Epidemiology and Prevention Res., [10]Med., [11]The Hotchkiss Brain Inst., [12]Libin Cardiovasc. Inst. of Alberta, [13]Fac. of Kinesology, Univ. of Calgary, Calgary, AB, Canada; [14]Psychiatry, Psychology & Neurosci., Dalhousie Univ., Halifax, NS, Canada

Abstract: Identifying risk factors for preventing or delaying the onset of dementia is currently an important public health campaign. Without effective intervention or treatment, the prevalence of dementia worldwide could exceed 135-million individuals by the year 2050. Physical inactivity, and associated risk factors such as obesity and cardiovascular disease, account for the majority of known modifiable risk factors for dementia . Additionally, individuals with a low brain reserve, defined as low educational and occupational attainment, fewer mentally stimulating leisure activities and lower intelligence, were at an 85% increased risk of dementia compared with individuals with high brain reserve . The Brain in Motion study (n = 220, 53% female) is investigating the effects of an aerobic exercise intervention on brain health in inactive older adults (aged 55- 85). The primary aim of the current cross-sectional analyses was to examine the impact of lifetime and current cognitive and physical activity on cognitive performance in healthy older adults. Cognitive function was determined using a standardized neuropsychological test battery, current fitness was measured using a treadmill test to determine maximal oxygen uptake (VO2max), and current and lifetime physical and cognitive activities were assessed using self-report questionnaires. Multivariate regression and correlations were used to determine if

current or lifetime physical activity, current or lifetime cognitive activity, and current fitness predicted objective cognitive performance. All analyses controlled for age, years of education and sex. Participants had, on average, 15.96 years of education. Average VO2max for the study population was 26.13. The regressions revealed that lifetime cognitive activity, but not lifetime physical activity, was a significant positive predictor of global cognitive performance (β= 0.17, SE= .002, p= .007). Increased diversity of current cognitive activity, but not current fitness or physical activity, was a significant predictor of greater global cognitive performance (β= 0.15, SE= .009, p= .009). Post-hoc analysis revealed greater verbal memory performance was best predicted by increased diversity of current cognitive activities (β= 0.13, SE= .02, p= .04). These data suggest that current and lifetime cognitive activity are good predictors of current global cognitive functioning. These findings suggest that engagement in a range of activities that stimulate cognitive function (e.g., reading, creative arts, volunteer work) may be important for maintaining cognitive function, at least in healthy and well-educated older adults.

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Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.16/B62

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant KL2 TR000095

Alzheimer’s Association New Investigator Grant NIRG-14-317353

Title: Altered functional connectivity of prefrontal cortex underpins the abnormality of intra-individual variability in reaction time in mild cognitive impairment

Authors: *P. REN, R. WU, M. MAPSTONE, F. LIN;
Univ. of Rochester, Rochester, NY

Abstract: Background: Intra-individual variability in reaction time (IIVRT) is often considered a hallmark of cognitive dysfunction and is abnormally larger in mild cognitive impairment (MCI) compared to healthy controls (HC). Converging evidence confirms the role of the prefrontal cortex (PFC) in atypical IIVRT. New evidence showing that dopamine impacts IIVRT suggests

that the PFC may work with other regions (e.g., basal ganglia) to regulate IIVRT. In the present study, two PFC-based neural connections (i.e., the executive control network (ECN) and fronto-basal ganglia circuitry) were examined in relation to IIVRT in the early neurodegenerative process. Methods: We conducted a case-control study in 11 MCI participants and 7 age-, education-, and sex-matched HC. Four executive control tests addressing different levels of cognitive load were used to generate IIVRT. We used task-free functional magnetic resonance imaging (fMRI) to assess the PFC-involved neural connections. Results: As expected, we found greater IIVRT in the MCI group compared to HCs. In the MCI group, IIVRT was positively correlated with the degree of connectivity in the fronto-basal ganglia circuit, and negatively correlated with the ECN in the right hemisphere. Conversely, IIVRT was negatively correlated with connectivity in fronto-basal ganglia circuit, and had no correlation with the ECN in the HC group. Conclusions: The altered relationship between IIVRT and two PFC-involved neural connections in MCI may indicate an early marker of the neurodegenerative process, though further work determining the causal link is needed.

Disclosures: **P. Ren:** None. **R. Wu:** None. **M. Mapstone:** None. **F. Lin:** None.

Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.17/B63

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Safety, tolerability and pharmacokinetics of a potent and selective 5-HT6 receptor antagonist, SUVN-502 following multiple ascending doses in healthy elderly humans, and effect of gender and food on single dose pharmacokinetics

Authors: ***R. V. NIROGI**, K. MUDIGONDA, K. PENTA, G. BHYRAPUNENI, D. AJJALA, N. MUDDANA, V. PALACHARLA, V. GOYAL, S. PANDEY, R. ABRAHAM, P. JAYARAJAN, R. KAMBHAMPATI, A. SHINDE;
Suven Life Sci., Hyderabad, India

Abstract: SUVN-502 and its active metabolite M1 of SUVN-502 are potent and selective 5-HT6 antagonists exhibiting cognitive enhancement in rodent models. SUVN-502 is being developed for the treatment of cognitive deficits associated with Alzheimer’s disease (AD). SUVN-502 was studied in a single-center, multi-faceted, phase 1 clinical trial (US IND) to evaluate its safety, tolerability, and pharmacokinetics after multiple ascending doses in healthy elderly male subjects. The effect of gender and food on SUVN-502 pharmacokinetics was also evaluated in

healthy subjects. SUVN-502 and its active metabolite M1 of SUVN-502 were quantified in plasma using a validated LC-MS/MS method. SUVN-502 was well tolerated up to the highest tested dose of 100 mg/day following single or repeated oral administration in healthy elderly male, and adult male and female subjects. There were no clinically relevant or serious adverse events. There was no significant effect of gender and food on the pharmacokinetics of SUVN-502 and M1 of SUVN-502 after single oral administration of 100 mg SUVN-502. SUVN-502 has shown a favorable safety and pharmacokinetic profile after single and repeated dose administration. SUVN-502 and M1 of SUVN-502 achieved the projected efficacy concentrations and attained steady state from the 7th day upon multiple administrations in elderly subjects. SUVN-502 is well tolerated in humans with adequate plasma exposure for efficacy, and favorable pharmacokinetics suitable for once a day oral administration.

Disclosures: R.V. Nirogi: A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **K. Mudigonda:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **K. Penta:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **G. Bhyrapuneni:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **D. Ajjala:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **N. Muddana:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **V. Palacharla:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **V. Goyal:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **S. Pandey:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **R. Abraham:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **R. Kambhampati:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **A. Shinde:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD.

Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.18/B64

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant 1R01AG042890

Title: S-nitroso-proteome in individuals naturally resistant to Alzheimer’s disease

Authors: *O. ZOLOCHEVSKA[1], N. L. BJORKLUND[2], R. L. WOLTJER[4], J. E. WIKTOROWICZ[3], G. TAGLIALATELA[1];

[1]Neurol., [2]Neurosci. and Cell Biol., [3]Biochem. & Mol. Biol., UTMB, Galveston, TX; [4]OHSU, Portland, OR

Abstract: Alzheimer's Disease (AD) is an age-dependent disorder which impairs cognition and results in memory loss, progressive dementia and ultimately - death. Synaptic loss and death of neurons in AD correlate with excessive oxidative and nitrosative stress. In AD, S-Nitrosylation (SNO) is involved in regulation of function of cytoskeletal, synaptic and mitochondrial proteins. Despite the established fact of SNO involvement in AD, its pathological significance remains poorly understood. Nevertheless, certain individuals remain cognitively intact despite the accumulation of amyloid beta (Abeta) and neurofibrillary tangles (hereafter termed Non-Demented with Alzheimer's Neuropathology - NDAN). The mechanisms responsible for preservation of cognitive function in NDAN are currently unknown, and understanding them will provide targets for novel, effective therapies. We have previously reported that the post-synaptic density (PSD) of NDAN subjects is resistant to Abeta binding, thus protecting synapses and preserving cognitive ability. Therefore, we hypothesize that the PSD of NDAN subjects has a unique protein signature (both in terms of protein levels and SNO protein modifications) that protects synapses from detrimental binding of Abeta. In order to test our hypothesis, we performed proteomics analysis of PSD fractions of hippocampi of control, AD and NDAN subjects. Our results identified 31 unique proteins that differ significantly between AD and NDAN. DAVID and PANTHER were used to analyze molecular functions of identified proteins. We identified 15 cytoskeletal proteins, 2 enzyme modulators, 2 hydrolases, 2 kinases, 1 ligase, 3 proteins involved in membrane traffic, 2 oxidoreductases, one protein participating in redox signaling, two Ca2+-binding proteins and one carrier protein. In order to evaluate the S-Nitroso-proteome of PSD fractions, we performed the biotin-switch technique, followed by MALDI TOF/TOF and SNOFlo. Our results showed 34 differentially S-Nitrosylated proteins in NDAN vs AD. Using DAVID and PANTHER we found that of these 43 proteins, 14 were cytoskeletal, one adhesion and one Ca2+-binding protein, one carrier protein, 3 hydrolases, one protein involved in immune response, 4 kinases, 3 proteins participating in membrane traffic, one mRNA polyadenylation factor, 3 oxidoreductases, one redox signaling protein and one transferase. Taken together, these findings suggest that the PSD of NDAN has a unique abundance and SNO-modification protein signature that could be involved in protecting synapses from Abeta toxicity, thus possibly contributing to allowing NDAN subjects to retain cognitive ability.

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Poster

761. Alzheimer's Neurodegeneration: Animal Models

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.19/B65

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Korea Institute of Oriental Medicine Grant K15310

Title: Impairment of intradimensional shift in an attentional set-shifting task in rats with chronic bilateral common carotid artery occlusion

Authors: *D.-H. KIM[1], B.-R. CHOI[1], W. JEON[2], J.-S. HAN[1];
[1]Konkuk Univ., Seoul, Korea, Republic of; [2]Korea Inst. of Oriental Med., Dae Jeon, Korea, Republic of

Abstract: Studies of rats with chronic bilateral common carotid artery occlusion (BCCAo), an animal model for vascular dementia (VaD), have reported hippocampus-dependent memory impairment and associated neuropathologies. It is reported that patients with VaD also have attentional shifting dysfunction. However, no study has done to reveal neural attentional impairment and its underlying alterations in brain structures responsible for attention, using animal model of VaD. Therefore, the present study examined attentional function in rats with BCCAo, using attentional set-shifting task (ASST) that required rats to choose a food-baited pot from two possible pots. ASST included 6 consecutive sessions including simple discrimination, compound discrimination, intradimensional shifting, extradimensional shifting, and reversals. The BCCAo rats were significantly slower at learning the intradimensional set-shifting task compared to control rats. Previous studies have demonstrated that the cingulate cortex and medial prefrontal cortex are critical to intradimensional and extradimensional set-shifting, respectively. Additionally, inflammatory responses and neuronal alterations were observed in rats with chronic BCCAo. In addition, the number of OX-6 positive microglia was significantly increased in the forceps minor white matter of BCCAo rats, and glutamate decarboxylase signals co-localized with NeuN were reduced in the anterior cingulate cortex of BCCAo rats, compared to control rats. Alterations of GABAergic neurons in the anterior cingulate cortex, damage to white matter, and attentional impairments observed in BCCAo rats suggest dysfunction of brain structures that are associated with attentional impairments observed in patients with VaD. This study was supported by a grant (K15310) from the Korea Institute of Oriental Medicine (KIOM).

Disclosures: **D. Kim:** None. **B. Choi:** None. **W. Jeon:** None. **J. Han:** None.

Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Indiana CTSI Collaboration in Translational Research

NIH/NIA R03 AG027123

American Parkinson Disease Association

Title: Role of aberrant expression of neuroprotective genes in DLB and other synucleinopathy disorders

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Abstract: Synucleinopathy disorders are characterized by the presence in post-mortem brains of Lewy body inclusions enriched with aggregated forms of the presynaptic protein alpha-synuclein (aSyn). Two examples of these diseases include dementia with Lewy bodies (DLB) and Parkinson's disease (PD). Pathogenic mechanisms underlying synucleinopathy disorders are poorly understood, and therapies targeting these diseases only temporarily relieve symptoms without slowing the underlying neurodegeneration. Here, we carried out a study aimed at determining the expression levels of a panel of candidate neuroprotective genes in post-mortem brain samples from DLB patients and age-matched controls (5 individuals in each group). mRNAs encoding the following proteins were quantified via qRT-PCR in homogenates prepared from cortex and cingulate gyrus: DJ-1, a protein with antioxidant and chaperone activities; PGC1-alpha, a master regulator of mitochondrial biogenesis and oxidative metabolism; MsrA, an antioxidant enzyme responsible for repairing oxidatively damaged proteins; and ATP13A2, a lysosomal protein involved in autophagy. In addition to yielding new insights into differential gene expression patterns in cortex versus cingulate gyrus, the data revealed differences in the expression levels of a subset of the mRNAs in DLB versus non-DLB cortical tissue. Notably, ATP13A2 mRNA levels were reduced in DLB cortex, and mRNAs encoding MsrA and PGC1-alpha showed trends towards being down-regulated. Additional studies revealed that aSyn neurotoxicity in primary midbrain cultures varies with the expression levels of each of these proteins. Collectively, our findings suggest that down-regulation of proteins involved in cellular antioxidant responses, mitochondrial function, and lysosomal autophagy contribute to

neurotoxicity in DLB and other synucleinopathies. Current efforts are aimed at mapping genome-wide epigenetic and transcriptional perturbations in DLB versus non-DLB brain tissue (our results suggest that genomic DNA is modestly hypomethylated in cortex and cingulate gyrus of DLB patients). These studies shed light on cellular pathways disrupted by aberrant gene expression in synucleinopathy disorders, and they set the stage for developing new therapeutic strategies.

Disclosures: P.C. Montenegro: None. **K.J. Head:** None. **B. Dehay:** None. **E. Bezard:** None. **J. Jelinek:** None. **Y. Liu:** None. **K.P. Nephew:** None. **J. Rochet:** None.

Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.21/B67

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: MOE ACRF Tier 2 Grant (MOE2012-T2-1-021)

Khoo Postdoctoral Fellowship Award (KPFA)(Duke-NUS-KPFA/2015/0001)

Title: Functional evaluation of dementia-associated mutations

Authors: *Q. YUAN[1,2,3], N. HUSAIN[1], H. S. JE[1,3];
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Abstract: Triad3A/RNF216 is an E3 ubiquitin ligase that ubiquitinates and degrade the activity-regulated cytoskeletal protein (Arc), a key neuronal protein that regulates basal excitatory synaptic transmission through the endocytosis of AMPA-type of glutamate receptor. Rare, missense substitutions in TRIAD3A gene are genetically linked with familial form of dementia, but have not been functionally evaluated. Here, we identified that missense substitutions in Triad3A (R660C and R694C) fail to ubiquitinate Arc and cannot rescue decreased excitatory synaptic strength that results from the knockdown of endogenous Triad3A in neurons. Intriguingly, this loss of function effects of Triad3A mutants was due to disrupted cellular localization and their lack of Arc interactions. Taken together, our results indicate that loss-of-function mutations in Triad3A may contribute to dementia phenotype by modulating basal synaptic transmission through lack of Triad3A-dependent, Arc degradation.

Disclosures: **Q. Yuan:** None. **N. Husain:** None. **H.S. Je:** None.

Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.22/B68

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Chronic treatment with dimethyl sulfoxide (DMSO) affects neuronal structure and function *in vivo*

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Abstract: Efficient drug delivery to the central nervous system is central for the treatment of cerebral diseases. However, a wide-range of potential drug candidates displays limited aqueous solubility, which complicates its delivery. One strategy to overcome this limitation is the systemic administration of these hydrophobic drugs in conjunction with an additive such as the aprotic chemical DMSO, which is widely used as a drug carrier. In clinical practices, DMSO is also directly used as treatment for traumatic brain injury or several forms of amyloidosis. Despite the commonly use of this solvent, the effects of DMSO on neuronal structure and activity remain poorly investigated and its potential additive effects to new drug candidates may be underestimated. Here, we addressed the question how chronic treatment with low dose of DMSO modulates synaptic plasticity in the presence or absence of a moderate level of beta-amyloid in a mouse model for presymptomatic Alzheimer’s disease (AD). To evaluate potential changes in synaptic connectivity, heterozygous APPSDL transgenic were crossed with homozygous EGFP expressing mice and dendritic spine morphology and density were evaluated in old male mice after oral self-administration of the drug. To explore effects on mice behavior, hippocampus-dependent and -independent learning performances were determined. We report that DMSO treatment significantly increases spine density on apical dendrites in the CA1 region of control animals and on basal dendrites in the CA3 region of APPSDL transgenic mice. Furthermore, we show that treatment with DMSO improves spatial memory performance and anxiety-like behavior in APPSDL transgenic animals. Therefore, we propose DMSO as a potential drug candidate for the prevention of amyloid beta-induced synaptotoxicity that contributes to cognitive and neuropathological symptoms in AD and other amyloidopathies.

Disclosures: **L. Penazzi:** None. **J. Lorengel:** None. **R. Brandt:** None. **L. Bakota:** None.

Poster

761. Alzheimer's Neurodegeneration: Animal Models

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Program#/Poster#: 761.23/B69

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: PO1AG014449

RO1AG043375

P30AG010161

P30AG019610

Title: Braak stage relevance to cognitive impairment in nondemented elderly

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Abstract: Recent AD diagnostic criteria and initiation of clinical prevention trials necessitate the need to identify non-cognitively impaired (NCI) individuals in the pre-clinical disease stage. Amyloid imaging and clinical neuropathological studies reveal a significant percentage of NCI cases have levels of amyloid deposition and Braak neurofibrillary tangle stages similar to those with mild cognitive impairment (MCI) and AD. Here we determined whether composite scores from a battery of cognitive tests differentiate subjects with a premortem clinical diagnosis of NCI who upon postmortem neuropathological evaluation displayed low and high Braak scores. Data was analyzed from 123 NCI individuals (63 males; mean age 83.90±6.12 yrs.) from the Religious Order Study. Individuals were grouped based on Braak stage (Low = 0 to II, High = III to VI) with a median Braak stage of III (range of 0 to V). Group differences on several cognitive composite scores were assessed to determine if individuals with higher Braak stages differed from those with lower Braak stages. Unadjusted analyses showed that High Braak cases performed significantly worse than Low Braak subjects on tests of the Semantic Memory domain ($p = 0.01$). Adjusting for age at death, gender, and education this difference was not statistically significant ($p = 0.21$). Analyses revealed a significant education by Braak stage interaction on Semantic Memory performance ($p = 0.02$). Similar associations between Braak stage and cognitive function were found when cases were grouped based upon NFTs mainly in the transentorhinal cortex (Braak stages 0, I and II), limbic cortex (stages III and IV), and neocortex (stages V and VI). No significant differences were found for Global Cognition, Episodic

Memory, Working Memory, Perceptual Speed, and Visuospatial performance. The significant interaction between education and Braak stage suggest that factors relating to cognitive reserve may play a role in the ability to detect cognitive changes or that NFT pathology is not a necessary precondition for cognitive impairment in pre-clinical AD.

Disclosures: **E.J. Mufson:** None. **M. Malek-Ahmadi:** None. **K. Chen:** None.

Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.24/B70

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: 5-HT6 antagonist SUVN-502 potentiates the procognitive and neurochemical effects of combined treatment with donepezil and memantine

Authors: R. MEDAPATTI, *P. JAYARAJAN, R. ABRAHAM, G. BHYRAPUNENI, V. BENADE, G. AYYANKI, R. VENKATESHWARLU, N. MUDDANA, R. PONNAMANENI, R. NIROGI;
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Abstract: Memory deficit is the most common symptom of Alzheimer’s disease. Memantine and donepezil are approved for the symptomatic treatment of cognitive deficits associated with Alzheimer’s disease (AD). Memantine added to stable donepezil in AD patients is associated with significant benefits in reducing decline in cognition, function and global status. SUVN-502 is a potent and selective 5-HT6 antagonist being developed for the symptomatic treatment of AD. We hypothesized that 5-HT6 antagonists may potentiate the therapeutic effects of memantine and donepezil. Therefore, the effect of SUVN-502 alone and in combination with memantine and donepezil was evaluated in object recognition task. The effect of the above combinations on the cholinergic neurotransmission was evaluated in the hippocampus of freely moving male Wistar rats using brain microdialysis. Co-treatment of SUVN-502, memantine and donepezil significantly potentiated the procognitive effects when compared with memantine and donepezil. Similarly co-treatment of SUVN-502 with memantine and donepezil significantly enhanced the acetylcholine levels in the hippocampus. The enhanced procognitive effects seen in the group co-treated with SUVN-502, memantine and donepezil can be attributed to the augmentation of the cholinergic neurotransmission in the brain. Thus combination of SUVN-502 with memantine and donepezil may offer a novel therapeutic strategy for the symptomatic treatment of AD.

Disclosures: **R. Medapatti:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **R. Abraham:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **G. Bhyrapuneni:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **V. Benade:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **G. Ayyanki:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **R. Venkateshwarlu:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **N. Muddana:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **R. Ponnamaneni:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences LTD.

Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.25/B71

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant 1R21AG042730-01A1

Title: Memory dysfunction in a rat model of Alzheimer’s disease

Authors: ***C. R. GALLOWAY**[1], M. L. AIREY[2], K. RAVIPATI[2], R. M. COHEN[3], A. I. LEVEY[4], J. R. MANNS[1];
[1]Psychology, [2]Neurosci. and Behavioral Biol. Program, [3]Psychiatry, [4]Neurol., Emory Univ., Atlanta, GA

Abstract: Alzheimer’s disease (AD) is a growing health problem that affects millions of people, but current treatment options are limited. Many new candidate drug treatments have demonstrated efficacy in transgenic mouse models of AD, but ultimately fail in the clinic. One potential reason for the difficulty in translating preclinical findings into viable drug treatments for AD may be due to the differences between pathological features of human AD, such as tau pathology and cell death, and the pathology of transgenic AD mouse models that do not show these features. Recently, a transgenic rat model of Alzheimer’s disease (TgF344 rats) with human APPSwe and PS1ΔE9 mutations was developed (Cohen et al., 2013, J. Neurosci., 33: 6245-6256). Like mouse models of AD, TgF344 rats develop age-dependent build-up of amyloid pathology, such as soluble Aβ42 and plaques. Unlike mouse models of AD, TgF344 rats also develop tau pathology and profound cell death, making them a good model to probe questions about AD that may be more readily translatable to human AD. Moreover, using a rat model of

AD will increase the feasibility of using high-density *in vivo* electrophysiology to answer questions about how hippocampal dysfunction contributes to memory loss symptoms in AD. It was previously shown that TgF344 rats had intact spatial memory performance at 6 months of age but performed poorly on a spatial memory task at 16 months. In order to further understand this rat model of AD, in the current study we asked at what age between 6 and 16 months the TgF344 rats would show memory impairments, and whether spatial memory and non-spatial memory would be differentially impaired. 16 female Tg344 rats were tested monthly, beginning at 5 months of age, on a non-spatial and a spatial recognition memory task. We found that TgF344 AD rats (n=8) had impaired spatial recognition memory performance by 9-12 months of age relative to wild-type (WT; n=8) littermate controls. In contrast, TgF344 AD rats performed similarly to WT controls on the spatial memory task from 5-8 months of age and on the non-spatial recognition memory task from 5-12 months. The selective memory impairment of TgF344 AD rats from 9-12 months supports an important role of spatial memory dysfunction relatively early in the disease process. Subsequent studies will use *in vivo* electrophysiological recordings in the hippocampus to ask if TgF344 AD rats have dysfunctional neural representations of space (e.g. "place fields"), and, if so, whether systemic administration of a muscarinic acetylcholine receptor agonist might attenuate the dysfunction.

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Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.26/B72

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CIHR Grant 101925

Title: Interaction between metabolic syndrome and Alzheimer's disease

Authors: *N. IVANOVA, N. WEISHAUPT, S. N. WHITEHEAD, D. F. CECHETTO; Anat. and Cell Biol., Western Univ., London, ON, Canada

Abstract: Accumulation of amyloid-β peptide and its cerebral deposition in a form of extracellular plaques are considered to be one of the major histopathological features of the Alzheimer's disease (AD). Insulin resistance and abnormal glucose metabolism, characteristics of type 2 diabetes and metabolic syndrome, has been also found to be implicated in

etiopathogenesis of AD linking these metabolic disorders with AD. Among other shared pathological mechanisms inflammation is of a great importance being one of the earliest processes contributing to cognitive decline prior to the plaque formation. Unhealthy lifestyle choice, particularly consumption of high-fat, high-sugar western type diets is a common risk factor for development of metabolic syndrome and increased incidence of clinical dementia. The existence of a common basis for these two pathologies raises the possibility of a contribution of metabolic disorders to the course of the dementia when these conditions are co-morbid, however, the underlying mechanisms of this interaction are yet to be elucidated. This study aims to investigate the co-morbid interaction between metabolic syndrome and AD and defining its role on the cognitive function in an aged co-morbid model of metabolic syndrome and AD. Male Fischer 344 wild type with intact genotype and transgenic overexpressing human β-amyloid precursor protein rats, 8.5-9 month old were maintained either on a hypercaloric western style diet with 40% energy from fat supplemented with 20% corn syrup drink or on control low-fat, low-sugar diet for 12 weeks. Metabolic changes were monitored using an intraperitoneal glucose tolerance test, blood lipid profile and insulin level analysis. Hypertension monitoring was performed using a non-invasive tail cuff method of blood pressure measurement. Spatial reference learning and memory were assessed using Morris water maze (MWM). Immunohistochemical staining was used to examine neuroinflammation and amyloid accumulation. Animals maintained on the western style diet developed significant obesity and metabolic changes. Results from the MWM demonstrated worsening cognitive performance trend in both co-morbid model of AD/metabolic syndrome and metabolic syndrome alone in the wild type animals. Immunohistochemical data have shown a greater neuroinflammation and amyloid deposition in the co-morbid model in comparison to metabolic syndrome alone. These results may be indicative of a possible mechanism of interaction between AD and metabolic syndrome.

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Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.27/B73

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Identification and characterization of a novel $GABA_A\alpha5$ negative allosteric modulator

Authors: M. NAKANISHI[1], S. KAWAHARADA[1], N. NAKANISHI[1], K. HAZAMA[1], H. MIYATA[1], M. HIGASHINO[1], A. LEWIS[2], G. CLARK[2], M. CHAMBERS[2], K. HIRST[2], S. MAIDMENT[2], A. RAE[2], G. WISHART[2], *A. KISHI[1], T. YASUHIRO[1], S. KATSUMATA[1]; [1]ONO Pharmaceut. Co., Ltd, Osaka, Japan; [2]BioFocus, Saffron Walden, United Kingdom

Abstract: Background: $GABA_A$ receptors are pentameric membrane proteins that gate chloride ions in response to binding of γ-aminobutyric acid (GABA). $GABA_A$ ion channels containing the α5 subunit ($GABA_A$α5) are highly expressed in hippocampus, the key area for cognitive processing. $GABA_A$α5 negative allosteric modulators (NAMs) enhance cognition in rodents. Similar phenotypes are observed in animals with point mutations of $GABA_A$α5. We identified orally available $GABA_A$α5 NAMs. **Methods:** Approximately 124,000 compounds were screened in both receptor binding and FLIPR functional assay in HEK-293 cell line stably expressing $GABA_A$α5. $GABA_A$α5 NAM activities of hit compounds were confirmed in electrophysiological assay. In the lead optimization phase, compounds with high binding affinity and selective $GABA_A$α5 NAM activity were evaluated in passive avoidance test, 8-arm radial maze test and novel object recognition test in rats. Anxiogenic-like and proconvulsant effects associated with non-selective $GABA_A$ NAM activity were also evaluated in rat elevated plus maze test and mouse PTZ test, respectively. General toxicity was evaluated by a 4-day repeated oral dose toxicity study in rats. **Results:** We identified an advanced lead compound with high affinity (Ki value = 7.9 nmol/L), NAM activity (EC_{50} = 1.1 nmol/L, Emax = -50%), and selectivity for α5 (Emax for $GABA_A$α1, 2 and 3 = -2%, 5% and -6%, respectively). Receptor occupancies in rat hippocampus were 44, 53, 71 and 89% at 1, 3, 10 and 20 mg/kg (p.o., 1 h), respectively. This agent (3, 10 and 20 mg/kg, p.o., 1h) significantly reversed MK-801-induced cognitive deficit in rat passive avoidance test. This agent (10 mg/kg, p.o., 1h) significantly reversed scopolamine/MK-801-induced cognitive deficit in rat 8-arm radial maze test. Moreover, this agent (10 mg/kg, p.o., 1h) significantly enhanced cognition in normal rat novel object recognition test. In rat hippocampus slice, this agent (300 nmol/L) significantly enhanced long term potentiation. This agent did not show anxiogenic-like or proconvulsant effects. In general toxicity study, this agent (30 mg/kg, p.o.) showed no obvious toxicological findings except for slight high values of plasma total cholesterol and phospholipid. **Conclusions:** We identified a novel, selective, orally available $GABA_A$α5 NAM which enhances cognition without anxiogenic or proconvulsant side effects.

Disclosures: M. Nakanishi: None. **S. Kawaharada:** None. **N. Nakanishi:** None. **K. Hazama:** None. **H. Miyata:** None. **M. Higashino:** None. **A. Lewis:** None. **G. Clark:** None. **M. Chambers:** None. **K. Hirst:** None. **S. Maidment:** None. **A. Rae:** None. **G. Wishart:** None. **A. Kishi:** None. **T. Yasuhiro:** None. **S. Katsumata:** None.

Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 761.28/B74

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Bright Focus Foundation

Title: ABCA7 variant and its impact on Alzheimer's disease

Authors: *J. VASQUEZ, S. ESTUS, J. SIMPSON;
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Abstract: Genome-wide association studies (GWAS) identify single nucleotide polymorphisms (SNPs) that associate with Alzheimer's disease (AD). Adenosine triphosphate binding cassette A7 (ABCA7) reached significance within several of these studies warranting investigation into this association. Rs200538373, within ABCA7, increases risk for AD in a process predicted to involve loss-of-function. Elucidating the mechanism of action for this increased AD risk may help to target this pathway effectively with pharmacological agents. Our overarching hypothesis is that rs200538373 modulates ABCA7 expression leading to decreased phagocytic clearance of amyloid-beta (Aβ). Here, we investigate the effects of rs200538373 at the molecular level. In preliminary results, we found that the minor allele of rs200538373 is associated with the extension of exon 41 into intron 41, thereby modulating the reading frame. In our current work, we are quantifying expression of both isoforms using qPCR to discern the extent that the atypical isoform is modulated by AD status, other SNPs, or cell type differences in the samples. In addition, we will use minigenes containing each allele to determine directly whether the AD-associated SNP modulates splicing. The results of these experiments will be presented in Chicago.

Disclosures: **J. Vasquez:** None. **S. Estus:** None. **J. Simpson:** None.

Poster

761. Alzheimer's Neurodegeneration: Animal Models

Location: Hall A

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CONACyT Grant 181323

DGAPA-UNAM Grant IN200715

DGAPA-UNAM Grant IN201415

Title: Amyloid β enhances typical rodent behavior while it impairs contextual memory consolidation

Authors: *K. G. SALGADO[1], F. PEÑA-ORTEGA[2], R. PRADO-ALCALÁ[2];
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Abstract: Alzheimer's disease (AD) is associated with an early hippocampal dysfunction, which is likely induced by an increase in soluble amyloid beta peptide (Aβ). This hippocampal failure contributes to the initial memory deficits observed both in patients and animal models, and possibly to the deterioration in activities of daily living (ADL). One typical rodent behavior that has been proposed as a hippocampus-dependent assessment model of ADL in mice and rats is burrowing. Despite the fact that AD transgenic mice show some evidence of reduced burrowing, it has not yet been determined whether or not Aβ can affect this typical rodent behavior and whether this alteration correlates with the well-known Aβ-induced memory impairment. Thus, the purpose of this study was to test whether or not Aβ affects burrowing while inducing hippocampus-dependent memory impairment. Surprisingly, our results show that intrahippocampal application of Aβ increases burrowing while inducing memory impairment. We consider that this Aβ-induced increase in burrowing might be associated with a mild anxiety state and conclude that Aβ-induced hippocampal dysfunction is reflected in a differential impairment of ADL and memory, through mechanisms yet to be determined.

Disclosures: K.G. Salgado: None. **F. Peña-Ortega:** None. **R. Prado-Alcalá:** None.

Poster

762. Parkinson's Disease: Rodent Models III

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 762.01/B76

Topic: C.03. Parkinson's Disease

Support: RRIA 2014 Grant ID 9784

Title: Contribution of neuroinflammation to Parkinson's disease in humanized immune system mice

Authors: *G. D. MANOCHA[1], K. L. PUIG[2], C. K. COMBS[3];
[1]Basic Sci., Univ. North Dakota, Grand Forks, ND; [2]Basic Sci., Univ. of North Dakota, Grand Forks, ND; [3]Basic Sci., Univ. of North Dakota, Grand forks, ND

Abstract: Reactive microglia have been associated with the histological changes that occur in Parkinson's disease brains and many mouse models of the disease. The presence of microgliosis during disease has been documented in many brain regions including the substantia nigra, striatum, hippocampus and various cortical areas. The rodent MPTP injection model of disease also produces striato-nigral microgliosis correlating with the loss of dopaminergic neurons. These findings support the notion that inflammatory changes contribute to cell loss during disease with the spectrum of change best characterized in rodent models. However, it is possible that immune responses in mice and humans may differ with respect to tissue or insult. In order to better profile specific inflammatory changes in the brain during human disease, we used female CD34+ humanized mice and the MPTP injection model. NSG mice engrafted with human CD34+ hematopoietic stem cells were injected with MPTP for comparison to MPTP injected C57BL/6 mice in order to quantify neuron loss, gliosis, inflammatory changes, and behavior. The mice were also treated with or without FK506 to quantify effects of immunomodulation on disease phenotype in each mouse line. MPTP injection produced the expected impairment of motor performance and tyrosine hydroxylase immunoreactivity in the substantia nigra and striatum of C57BL/6 mice with minimal effect of FK506 treatment. A similar decrease in tyrosine hydroxylase immunoreactivity and motor performance was observed in the MPTP injected CD34+ humanized mice demonstrating conservation of toxin-mediated neuron death in this line. More importantly, FK605 treatment had a dramatic effect on improving behavior performance but not tyrosine hydroxylase immunoreactivity in these mice. As expected, MPTP injection produced a significant increase in Iba-1 positive microglial staining in the striatum and substantia nigra of both mouse lines with FK506-mediated attenuation in the CD34+ humanized mice. These data demonstrate differences in the MPTP injection model of PD between female C57BL/6 and CD34+ humanized mice with a significant benefit of immunomodulation in the later.

Disclosures: G.D. Manocha: None. **K.L. Puig:** None. **C.K. Combs:** None.

Poster

762. Parkinson's Disease: Rodent Models III

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 762.02/B77

Topic: C.03. Parkinson's Disease

Support: DFG Research Center for Nanoscale Microscopy and Molecular Physiology of the Brain (CNMPB), Goettingen, Germany

Title: The ROCK inhibitor fasudil alters alpha-synuclein aggregation *in vitro* and improves motor and cognitive behavior in alpha-synuclein.A53T.tg mice *in vivo*

Authors: *L. TATENHORST[1], H. WALLE[1], K. ECKERMANN[1], V. DAMBECK[1], L. FONSECA[3], T. LOPES DA FONSECA[2], J. C. KOCH[1], L. TÖNGES[1], M. BÄHR[1,4], T. F. OUTEIRO[2,4], M. ZWECKSTETTER[3,4], P. LINGOR[1,4];
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Abstract: Parkinson's disease (PD) is the most common neurodegenerative movement disorder. Rho kinase (ROCK) was recently described as a novel molecular neuroprotective target in PD. Since alpha-synuclein (αSyn) aggregation is a major pathophysiological step in the development of PD, we aimed to evaluate the anti-aggregative potential of pharmacological ROCK inhibition using the isoquinoline derivative Fasudil, a small molecule inhibitor already approved for clinical human use. In a cell-free aggregation assay, Fasudil treatment significantly delayed αSyn aggregation and inhibited fibril formation. NMR spectroscopy revealed a direct binding of Fasudil to two tyrosin residues in the C-terminal region of αSyn. In a cell culture aggregation model using double transfection with synphilin-1 (SYPH1) and carboxy-terminally truncated αSyn (synT) in H4 human neuroglioma cells *in vitro*, the number of intracellular SYPH1/synT aggregates was significantly reduced after Fasudil treatment. Interestingly, site-directed mutagenesis against the C-terminal tyrosine residues abolished this effect. Furthermore, size-exclusion chromatography (SEC)-HPLC followed by dotblot analysis of synT indicated a shift towards smaller synT aggregates in the H4 model after Fasudil treatment. We then evaluated the impact of long-term Fasudil treatment on αSyn pathology *in vivo* using a transgenic mouse model expressing human αSyn.A53T. Fasudil treatment did not show any deleterious side effects. Motor behavior investigated by Catwalk gait analysis was significantly improved after Fasudil treatment. Additionally, Fasudil treatment improved recognition memory of αSyn.A53T mice as detected in the novel object recognition (NOR) test. Overall survival of αSyn.A53T mice treated with Fasudil was not significantly altered. Our data show that pharmacological ROCK inhibition directly alters αSyn aggregation in cell free as well as cell culture models *in vitro*, and improved motor behavior and cognition after long-term treatment in αSyn.A53T mice. This strengthens the value of Fasudil as a highly promising pharmacological candidate for disease-modifying therapies for PD.

Disclosures: **L. Tatenhorst:** None. **H. Walle:** None. **K. Eckermann:** None. **V. Dambeck:** None. **L. Fonseca:** None. **T. Lopes da Fonseca:** None. **J.C. Koch:** None. **L. Tönges:** None. **M. Bähr:** None. **T.F. Outeiro:** None. **M. Zweckstetter:** None. **P. Lingor:** None.

Poster

762. Parkinson's Disease: Rodent Models III

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 762.03/B78

Topic: C.03. Parkinson's Disease

Title: Glucocerebrosidase modulates cognitive and motor activities in Parkinson's disease mouse models

Authors: J. CLARKE[1], E. ROCKENSTEIN[2], C. VIEL[1], C. TRELEAVEN[1], C. KIM[2], B. SPENCER[2], A. ADAME[2], H. PARK[1], J. DODGE[1], S. CHENG[1], L. SHIHABUDDIN[1], E. MASLIAH[2], *S. SARDI[1];
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Abstract: Heterozygous mutations of GBA1, the gene encoding glucocerebrosidase, represent the highest genetic risk factor for developing synucleinopathies such as Parkinson's disease (PD) and dementia with Lewy bodies (DLB). PD patients carrying mutated GBA1 alleles present a higher prevalence and severity of motor and non-motor symptoms, suggesting a link between the enzyme and the development of the disease. Furthermore, PD patients with or without GBA1 mutations also exhibit lower enzymatic levels of glucocerebrosidase in the central nervous system (CNS), thus implicating this lysosomal enzyme in the disease pathogenesis. However, the mechanisms by which GBA1 mutations lead to synucleinopathies remain unclear. The present studies demonstrate that reduction of glucocerebrosidase activity lead to α-synuclein accumulation and behavioral aberrations in the absence of GBA1 mutations. Partial glucocerebrosidase inhibition with CBE induced cognitive and motor deficits in the PrP-A53T-SNCA transgenic mouse accompanied by profound increase in α-synuclein. Conversely, augmenting glucocerebrosidase activity modulate synucleinopathy progression in the Thy1-SNCA mouse model of PD. Using gene therapy to increase glucocerebrosidase activity led to a decrease in proteinase K-resistant α-synuclein accumulation, amelioration of behavioral aberrations and prevention of dopaminergic loss. The data confirm that increasing glycosidase activity can modulate α-synuclein processing and reduce the progression of synucleinopathies. Collectively, these findings provide the first *in vivo* validation for augmenting

glucocerebrosidase activity in the CNS as potential therapeutic strategy for Parkinson's, regardless of the GBA1 mutation status.

Disclosures: **J. Clarke:** A. Employment/Salary (full or part-time):; Genzyme, a Sanofi Co. **E. Rockenstein:** None. **C. Viel:** A. Employment/Salary (full or part-time):; Genzyme, a Sanofi Co. **C. Treleaven:** A. Employment/Salary (full or part-time):; Genzyme, a Sanofi Co. **C. Kim:** None. **B. Spencer:** None. **A. Adame:** None. **H. Park:** A. Employment/Salary (full or part-time):; Genzyme, a Sanofi Co. **J. Dodge:** A. Employment/Salary (full or part-time):; Genzyme, a Sanofi Co. **S. Cheng:** A. Employment/Salary (full or part-time):; Genzyme, a Sanofi Co. **L. Shihabuddin:** A. Employment/Salary (full or part-time):; Genzyme, a Sanofi Co. **E. Masliah:** None. **S. Sardi:** A. Employment/Salary (full or part-time):; Genzyme, a Sanofi Co.

Poster

762. Parkinson's Disease: Rodent Models III

Location: Hall A

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Topic: C.03. Parkinson's Disease

Support: Parkinson's Disease Foundation (IRGP 09-11)

Royal Society (2006/R1)

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Ellison Medical Foundation

Title: The role of neuronal peroxisome proliferator-activated receptors in the MPTP mouse model of Parkinson's disease

Authors: ***P. TEISMANN**[1], R. B. MOUNSEY[1], H. L. MARTIN[1], M. C. NELSON[2], R. M. EVANS[2];
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Abstract: Background. Parkinson's disease (PD) is a progressive neurodegenerative disorder which can be modelled by the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Neuroinflammation has long been implicated in the disease process. Activation of peroxisome proliferator-activated receptors (PPAR), namely PPARγ and PPARδ, has been shown to provide neuroprotection in PD, and the observed effect has been linked to anti-oxidant and anti-inflammatory effects of the PPARs. Objective. Herein we addressed the role of neuronal expressed PPARs in the MPTP-model of PD. Methods. Mice null for neuronal expressed PPARγ and/or PPARδ received a sub-acute regimen of MPTP (30mg/kg i.p., over 5 consecutive days). Expression of PPARγ and PPARδ was assessed by immunofluorescence. 21 days after MPTP, striatal optical density, striatal dopamine content and number of surviving dopaminergic neurons in the SNpc was assessed. Results. Presence of one or both these receptors show a trend toward protection against MPTP-induced neurodegeneration as higher dopaminergic cell immunoreactivity and striatal monoamine levels are evident. Although not significant, mice null for both receptors show the lowest levels of TH-positive cell bodies following MPTP administration (3033 ± 531 compared to wt controls: 4135 ± 766). Conclusion. This data supplements recent studies that have elected to use agonists of the receptors to regulate immune responses. The results place further importance on the activation of PPARs and the neuroprotective roles these have in inflammatory processes linked to neurodegenerative processes. But our studies show that the main protective role is played by glial rather than neuronal receptors, which will need further evaluation.

Disclosures: P. Teismann: None. **R.B. Mounsey:** None. **H.L. Martin:** None. **M.C. Nelson:** None. **R.M. Evans:** None.

Poster

762. Parkinson's Disease: Rodent Models III

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Program#/Poster#: 762.05/B80

Topic: C.03. Parkinson's Disease

Support: Funded by Boehringer Ingelheim Pharma GmbH & Co KG

Title: Development of a leucine-rich repeat kinase 2 *in vivo* Parkinson's disease model by stereotactic intracranial injection of high-capacity adenoviral vectors

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Abstract: Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are the most common genetic cause of Parkinson's disease. The most prevalent mutation, G2019S, leads to increased kinase activity, which appears to be cytotoxic for neurons. LRRK2 animal models are of significant value for research to test therapeutic LRRK2 inhibitors counteracting the toxic impact of LRRK2_G2019S and to uncover general mechanisms underlying the development of Parkinson's disease. Only two out of five published LRRK2_G2019S transgenic rodent models, however, showed the hallmark of Parkinson's disease, which is degeneration of dopaminergic neurons (Ramonet et al., 2011; Chen et al., 2012; Li et al., 2010; Melrose et al., 2010; Zhou et al., 2011). Viral vectors are an alternative approach to introduce LRRK2_G2019S into the brain and they might be more successful in inducing neurodegeneration (Dusonchet et al., 2011; Lee et al., 2010; Tsika et al., 2015). One caveat with these viral vector based models is, however, that transgene expression decreases over time, likely due to immunologic clearance of transduced cells in response to low level expression of viral genes. We aim to develop a LRRK2_G2019S Parkinson's disease mouse model by stereotactic intracranial injection of high-capacity adenoviral vectors. This vector type lacks any viral coding sequences, thereby being an ideal tool to achieve long-term expression of delivered transgenes. We designed and generated high-capacity adenoviral vectors encoding either LRRK2_G2019S or the kinase-dead mutant LRRK2_D1994A. Since it is not known whether LRRK2_G2019S expression in neurons themselves or in surrounding glia is the trigger for neurodegeneration *in vivo*, we make use of two different promoters: the neuron-specific human synapsin promoter and the ubiquitously active chicken β-actin (CAG) promoter. To determine an optimal dose for intracranial injection resulting in efficient transduction and transgene expression without significant virus-mediated neuroinflammation, CAG-LRRK2 vectors were titrated in the mouse striatum. Immunohistochemical analysis showed that injection of 1.3E+08 vector particles lead to severe neuroinflammation accompanied by a loss of LRRK2 expression within three weeks. In contrast, we observed widespread LRRK2 expression and only mild neuroinflammation at low vectors doses between 1 and 4.3E+07 particles. After further refinement of vector dosage we will perform long-term studies on vector-injected mice. Behavioral, biochemical and immunohistochemical analyses will be employed to show if Parkinson's disease can be mimicked in this high-capacity adenoviral LRRK2-vector based mouse model.

Disclosures: **A. Kritzinger:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Boehringer Ingelheim Pharma GmbH & Co KG. **T. Ciossek:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co KG. **B. Ferger:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co KG. **S. Kochanek:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Boehringer Ingelheim Pharma GmbH & Co KG.

Poster

762. Parkinson's Disease: Rodent Models III

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 762.06/B81

Topic: C.03. Parkinson’s Disease

Support: NIH/NINDS NS077022

Gardner Family Center for Parkinson's Disease and Movement Disorders

University of Cincinnati Neuroscience Institute

Title: Loss of ATP13A2 function accelerates the behavioral phenotype in mice that overexpress human wildtype alpha-synuclein

Authors: E. DIRR[1], R. BLACKWOOD[1], N. SANTIAGO[1], E. DEVINE[1], E. MASLIAH[4], P. SCHULTHEIS[5], G. SHULL[2], Y. SUN[6], M. ROMERO-RAMOS[7], P.-O. FERNAGUT[8], E. BEZARD[8], B. DEHAY[8], *S. M. FLEMING[3];
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Abstract: Loss of function mutations in the gene ATP13A2 are associated with Kufor-Rakeb Syndrome and Neuronal Ceroid Lipofuscinosis. The former is designated as a rare inherited form of Parkinson’s disease (PD). The function of ATP13A2 is unclear but *in vitro* studies suggest that it is involved in the lysosomal degradation of proteins and in the homeostasis of manganese and zinc. We recently showed that ATP13A2-deficient (13a2) mice develop age-dependent sensorimotor deficits, and enhanced lipofuscinosis and accumulation of insoluble alpha-synuclein (aSyn) in the brain. The presynaptic protein aSyn abnormally accumulates in PD and is degraded in part through lysosomal-autophagy degradation pathways suggesting the relationship between ATP13A2 and aSyn may be important in PD. In order to better understand the function of ATP13A2 and its interaction with aSyn we developed double mutant mice that are ATP13A2 deficient (13a2) and overexpress human wildtype aSyn (aSyn). Female and male wildtype (WT), 13a2, aSyn, and 13a2-aSyn mice were tested on a battery of sensorimotor and non-motor tests including the challenging beam traversal test, spontaneous and locomotor activity, nest building, gait, object recognition, and elevated plus maze. Sensorimotor tests were performed at 2, 4, and 6 months (m) of age, while object recognition and elevated plus maze were performed at 2 and 6

months. At 2m of age female 13a2-aSyn mice displayed significant impairments on the challenging beam compared to WT mice while 13a2 and aSyn mice did not differ from WT. In addition, the impairment was progressive with 13a2-aSyn at 6m making significantly more errors compared to 13a2-aSyn at 2m. Similarly, 13a2-aSyn mice displayed increased locomotor activity at 2m compared to WT while 13a2 and aSyn mice did not differ from WT. An effect of the double mutation was also observed in the elevated plus maze. At 6m 13a2-aSyn mice spent significantly more time in the open arm compared to WT while 13a2 and aSyn did not differ from WT. These results indicate that loss of ATP13A2 function accelerates the behavioral phenotype in aSyn mice. Analysis of autophagy markers, aSyn, neuronal integrity, and microglial response are currently ongoing.

Disclosures: **E. Dirr:** None. **R. Blackwood:** None. **N. Santiago:** None. **E. Devine:** None. **E. Masliah:** None. **P. Schultheis:** None. **G. Shull:** None. **Y. Sun:** None. **M. Romero-Ramos:** None. **P. Fernagut:** None. **E. Bezard:** None. **B. Dehay:** None. **S.M. Fleming:** None.

Poster

762. Parkinson's Disease: Rodent Models III

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 762.07/B82

Topic: C.03. Parkinson’s Disease

Title: Complementary phenotypic characterization of two genetically modified animal models of Parkinson’s disease: Line 61 and Line D

Authors: *S. RAMBOZ, K. CIRILLO, R. SPRINGER, M. MAZZELLA, M. WINDISCH, K. WALKER;
Psychogenics Inc., Tarrytown, NY

Abstract: Numerous genetic and pharmacological animal models have been generated to mimic different aspects of Parkinson’s disease, a neurodegenerative disorder estimated to affect more than 1% of the over-65 population. Parkinson’s disease is associated with the loss of nigral dopaminergic cells leading to a decline in dopamine levels. Due to this observation, depletion of nigral dopaminergic cells using lesion models have been developed and used to investigate the basis of symptomatic treatment. In the last couple of years, PsychoGenics has established and validated lesions models of MPTP and 6OHDA which are broadly used to assess neuroprotective drug treatments. Like any model, the lesions have a down side, provoking a very rapid loss of dopaminergic neurons, which would have taken decades in human. Slow cell loss and dopamine depletion would allow some compensatory mechanisms to take place, which might be not

present in the lesion models. Recently, PsychoGenics licensed a well described and validated genetically modified α-synuclein mouse line from Prof. Masliah's laboratory at UCSD: Line 61. This line is α-synuclein transgenic mouse model expressing the human α-synuclein cDNA under the murine Thy-1 promoter . Line 61 presents most of the characteristics of parkinsonism symptoms, including lack of coordination at 4 months, cognition deficit at 4.5 months, increased of total activity in open field by 7 months, hypolocomotion by 14 months and presence of α-synuclein positive aggregates. By 9 months of age, accumulation of phosphorylated Serine 129 residues in striatum and substantia nigra which might modulate the formation of protein aggregation likes inclusion bodies and fibrils. We are assessing the line 61 animal model using PsychoGenics proprietary technologies (SmartCube®, PhenoCube® and NeuroCube®) to retrieve early onset phenotype and establish high throughput preclinical readouts.

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Poster

762. Parkinson's Disease: Rodent Models III

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 762.08/B83

Topic: C.03. Parkinson's Disease

Title: Dysregulated macroautophagy and mitochondrial dynamics in pd with glucocerebrosidase mutations

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Abstract: Glucocerebrosidase (GBA) is a lysosomal hydrolase. While homozygous GBA mutations result in Gaucher disease (GD), a prototypic lysosomal storage disorder, heterozygous GBA mutations are associated with α -synuclein aggregation disorders ("synucleinopathies"), including Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Both homozygous and heterozygous GBA mutations produce an approximately 20-fold increase in the risk for PD. Recent studies provide mechanistic links between the GBA mutations and PD, including α -synuclein aggregation, lysosome and mitochondrial dysfunction. In the present study, we have examined fibroblasts from 8 controls and 8 GBA mutant PD (GBA-PD) patients for autophagy signaling and mitochondrial function/dynamics. In GBA-PD patients, GBA protein level is decreased by 30%, and the GBA enzyme activity is reduced by 45.5 %. Autophagy is suppressed in GBA-PD fibroblasts, as indicated by a decrease in LC3-II and an increase in P62 protein.

Consequently, we find an accumulation of mitochondria mass which is manifested by increased protein levels of Tom20 and porin, two mitochondrial membrane protein. Consistently, we find that mitochondria membrane potential decreases slightly and mitochondria reactive oxygen species accumulate in GBA-PD fibroblasts. We also detect an increase in protein levels of Mfn2 and Opa1 in GBA-PD patient fibroblasts, as well as GBA L444P heterozygous mouse brain, suggesting altered balance in mitochondria fission and fusion in response to GBA mutations. These observations indicate that GBA deficiency can interrupt autophagy pathway and lead to impaired energy and free radical homeostasis.

Disclosures: H. Li: None. **A. Ham:** None. **M. Cheng:** None. **Y. Quan:** None. **S. Kuo:** None. **G. Tang:** None.

Poster

762. Parkinson's Disease: Rodent Models III

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Program#/Poster#: 762.09/B84

Topic: C.03. Parkinson’s Disease

Support: Michael J. Fox Foundation

Title: Loss of striatal mitochondrial mitoNEET leads to a Parkinson’s disease phenotype in mice

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Abstract: Parkinson’s disease (PD) is an age-associated neurodegenerative disease which affects the dopaminergic neurons in the substantia nigra. The loss of the neurotransmitter dopamine (DA) leads to the characteristic movement symptoms seen in PD. Mitochondrial dysfunction is thought to contribute to the pathology of the neuronal cell death in PD. Here we describe the effect of loss of the mitochondrial membrane protein mitoNEET in a novel PD model. We found that mice null for mitoNEET showed a significant decrease in DA as well as tyrosine hydroxylase levels in the striatum. Mitophagy was significantly affected in the mice null for mitoNEET with markers such as LC3 and P62 greatly reduced. Additionally we found significant increases in protein misfolding as seen from Congo Red histology of striatal brain section in five month old mice. Compared to mice with the transgenic strain FVB/NJ-Tg(Slc6a3-PARK2*Q311X)AXwy/J, where the mice express the mutant human parkin gene (PARK2) carrying the Q311X truncation associated with Turkish early-onset PD, mice null for mitoNEET

showed increased levels of reactive oxygen species in the striatum. Behavioral analysis using a battery of tests showed that mice null for mitoNEET had shorter stride lengths and were more prone to fall during a rota-rod assay. In conclusion, our data here indicates that mitochondrial dysfunction in the mitoNEET null mice contributes to a PD phenotype in the mice. Support: Michael J. Fox Foundation

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Poster

762. Parkinson's Disease: Rodent Models III

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 762.10/B85

Topic: C.03. Parkinson’s Disease

Support: Merck-Serono

Title: Behavioural and histopathological characterization of mice with glucocerebrosidase knock-out in dopaminergic neurons

Authors: *P.-O. FERNAGUT[1], M. ENGELN[1], S. DOVERO[1], F. N. SORIA[1], B. DEHAY[1], E. NORMAND[2], M. MARTINEZ-VICENTE[3], C. GLANGETAS[2], F. GEORGES[2], M. VILA[3], C. LO BIANCO[4], E. BEZARD[1];
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Abstract: Mutations in the GBA1 gene encoding the lysosomal enzyme glucocerebrosidase (GBA) are an important risk factor for Parkinson’s disease. Altered GBA activity promotes alpha-synuclein accumulation and elevated levels of alpha-synuclein compromise GBA enzymatic function, thus supporting a pathogenic mechanism in PD. Because knock-out of GBA1 in the whole central nervous system in mouse induces massive neurodegeneration associated with early death, we sought to generate a mouse model of dopaminergic GBA deficiency to investigate the long-term consequences of compromised GBA function. Mice

expressing Cre recombinase under the control of the dopamine transporter promoter (DAT) were crossed with mice where GBA1 is flanked with two loxP sites between exons 9 and 11 in order to obtain animals with a selective disruption of GBA in dopaminergic neurons. DAT-GBA KO mice were assessed for motor function (pole test, challenging beam task), striatal neurochemistry, nigral lysosomal function, alpha-synuclein accumulation and number of dopaminergic neurons. DAT-GBA KO mice did not display motor impairments up to 12 month old. Lysosomal activity (beta-hexosaminidase, alkaline phosphatase, and cathepsin D) was unaffected in 4 month-old DAT-GBA KO followed with increased activity at 14 months. HPLC analysis of striatal levels of dopamine (DA) and metabolites revealed normal DA tissue content in DAT-GBA KO mice at 8 months, although there was a trend for reduced DOPAC levels and DA turnover. Histopathology revealed no significant effect of GBA deficiency in mice aged 8 months regarding alpha-synuclein accumulation and stereological counts of tyrosine hydroxylase-positive neurons in the substantia nigra. Whether nigral GBA deficiency affects dopaminergic neurodegeneration induced by viral-mediated overexpression of alpha-synuclein is currently being tested. Together, these results suggest that dopaminergic GBA deficiency in young to mature mice does not lead to detrimental effects on motor function and dopaminergic neurons in those young to mature animals.

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Poster

762. Parkinson's Disease: Rodent Models III

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 762.11/B86

Topic: C.03. Parkinson’s Disease

Title: Targeting GBA1 for Parkinson’s disease research

Authors: *K. D. DAVE[1], A. K. MARTIG[1], T. N. MARTINEZ[1], L. J. PELLEGRINO[2], L. B. DUNGAN[2], R. HAMLER[2], S. W. CLARK[2], P. D. BUCKETT[3], Y. CHEN[3], W. SHAN[3], W. D. HIRST[3], M. SASNER[4], M. HERBERTH[5], R. SWITZER[6], T. B. SHERER[1], B. K. FISKE[1]; [1]Res., The Michael J. Fox Fndn. For Parkinson's Res., New York, NY; [2]Amicus Therapeut.,

Cranbury, NJ; [3]Pfizer, Boston, MA; [4]The Jackson Lab., Bar Harbor, ME; [5]WIL Res., Ashland, OH; [6]NeuroScience Associates, Knoxville, TN

Abstract: Heterozygous mutations in the GBA1 gene, which encodes for lysosomal glucocerebrosidase (GCase), have been identified as the most common genetic risk factor for Parkinson's disease (PD). Decreased GCase activity has been reported in PD patients, in both genetic as well as in sporadic cases and emerging experimental evidence suggests a correlation between this decreased activity and accumulation of alpha-synuclein (aSyn). These strong genetic and pathological links make GCase an attractive target for PD drug development. As such, The Michael J. Fox Foundation (MJFF) has made robust investments to address key questions to effectively translate GCase therapeutically for PD patients. First, are GBA1 mutations relevant to sporadic Parkinson's and could a therapeutic directed against GBA1-mediated Parkinson's be efficacious for general PD population? To address this challenge, MJFF has funded biomarker studies in samples from sporadic patients to determine how GCase levels/activity and lipid substrates relate to aSyn burden and disease severity. Also, MJFF initiated recruitment of 250 GBA1 (125 affected and 125 unaffected) mutation carriers to the Parkinson's Progression Markers Initiative to identify GBA1-related biomarkers and inform our understanding of the natural history of PD. Second, the hypothesis that reduced GCase activity is causative of PD via aSyn accumulation needs to be confirmed. To address this issue, MJFF has funded generation of animal models and tools that would aid in studying the reciprocal relationship between GCase and aSyn, and for testing efficacy. The GBA1 D409V knock in mouse model developed in collaboration with MJFF's Industry Tools Consortium shows a gene dose-dependent reduction in GCase activity and a corresponding increase in substrate accumulation. MJFF is further characterizing this model by crossing it with an aSyn transgenic mouse to determine if loss of GBA1 function affects aSyn induced pathology and related phenotypes. Third, it remains unclear what is the most optimal approach to target GCase therapeutically. To this end, MJFF has funded diverse programs to increase GCase activity to possibly slow disease progression and "reverse" synuclein-related pathological manifestations of the disease. This includes therapeutic programs which increase stabilization and lysosomal translocation of GCase or direct activation of GCase, which would increase the levels of functional enzyme in lysosomes. MJFF's vision is to apply a holistic strategy to address research and therapeutic challenges to enable accelerated development of GBA1-targeting therapeutics and optimally informed clinical trials.

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Poster

762. Parkinson's Disease: Rodent Models III

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 762.12/B87

Topic: C.03. Parkinson's Disease

Title: The effect of aging on catecholamines and purines levels in the basal ganglia of mice carrying the A53T and A30P alpha-synuclein mutations

Authors: A. K. PANI, D. B. LESTER, A. KORFF, *Y. JIAO, R. J. SMEYNE;
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Abstract: The risk of developing Parkinson's disease increases with age. Although Parkinson's disease causation is multifactor in nature, a number of genes have been implicated in its genesis including the gene encoding alpha-synuclein (SNCA). Mutations in SNCA lead to an autosomal dominant form of parkinsonism, and the two most common mutations are A53T and A30P. Although there are many documented effects of these mutations, their effect on purine and catecholamine levels in the basal ganglia during aging have not been documented. Understanding how these levels change during aging is important since adenosine is known to be involved in modulation of the ATP pools (energy within the cell). Adenosine also acts as a non-classical inhibitory neurotransmitter and neuromodulator, that has been shown to act on catecholamine's, especially on dopamine levels and dopamine synthesis and turnover; two critical factors that underlie many of the motor symptoms in Parkinson's disease. Within the brain, purinergic levels are the combination of the additive actions of adenosine formation and breakdown; and thus are only a snapshot of total content of adenosine. The formation of adenosine is controlled by the enzymatic activity of intracellular and extracellular AMP-selective 5' nucleotidases that catalyze the breakdown of ADP and AMP. To determine if there are age-related alterations in these purine pools, we used the liquid- chromatographic techniques with an electrochemical detector to examine adenosine, ATP, ADP and AMP levels simultaneously, in the basal ganglia of wild-type mice as well as mice carrying mutations in the alpha-synuclein gene (A53T and A30P and SNCA-/-) at 4, 12, 18 and/or 24 months. The evaluation of striatal adenosine levels shows significant changes between WT and alpha-synuclein at each age examined. ATP alterations are seen in 4-month mice, while ADP changes are only seen at 24 months. No significant differences were observed in striatal AMP at any age. In the SN, adenosine levels shows significant changes between WT and alpha-synuclein at 12 and 24 months, while ATP changes are seen at 12 months, ADP changes are seen at 4, 12 and 24 months and AMP changes are seen at 12 and 24 months. The age-related alterations to purinergic contents will be compared with aminergic levels in the basal ganglia of mice carrying the A53T and A30P alpha-synuclein mutations.

Disclosures: **A.K. Pani:** None. **D.B. Lester:** None. **A. Korff:** None. **Y. Jiao:** None. **R.J. Smeyne:** None.

Poster

762. Parkinson's Disease: Rodent Models III

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 762.13/B88

Topic: C.03. Parkinson's Disease

Title: The accelerating rotarod is a more sensitive test for detecting dopamine-related loss of motor function than automated gait analysis

Authors: *D. ANDERSSON, M. RONILD, J. FULLERTON STØIER;
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Abstract: The MitoPark (+/DAT-cre, TfamloxP/TfamloxP) mouse model is a progressive model of dopamine (DA) loss brought about by the conditional knock-out of the mitochondrial transcription factor A (Tfam). This transgene results in a gradual loss of DA neurons, resulting in a motor phenotype that develops gradually. In this study, we have evaluated the motor function of these mice by means of the accelerating rotarod test and the CatWalk, an automated gait analysis system (Noldus, Wageningen, The Netherlands). We repeatedly (once a week) tested Mitopark mice and littermate control mice (carrying one floxed copy of Tfam) in the two assays from a relatively early age (when motor function was similar in the two groups) and onwards until MitoPark mice developed a clear deficit in the respective assay. In parallel, we also evaluated the striatal dopamine content at various ages in order to create a timeline of DA loss. In addition, we were also able to completely reverse the deficits in the respective assays via treatment with the DA precursor L-3,4-dihydroxyphenylalanine (L-DOPA), demonstrating the DA-dependence of the respective phenotypes. Our results indicate that the rotarod deficit starts developing at around 10-11 weeks of age, when striatal DA levels are at around 30% of that in the littermate control mice. In contrast, the gait deficits as measured by CatWalk appear at a more advanced age (approximately 14-15 weeks), when DA levels are projected to be around 15-20%. In summary, the results of the current study indicate that while automated gait analysis allows for a more detailed investigation of the nature of gait deficits, measuring maximal motor performance via the accelerating rotarod constitutes a more sensitive method for detecting motor deficits related to loss of striatal DA levels.

Disclosures: **D. Andersson:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S. **M. Ronild:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S. **J. Fullerton Støier:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S.

Poster

762. Parkinson's Disease: Rodent Models III

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 762.14/B89

Topic: C.03. Parkinson's Disease

Support: CIHR

Title: Sex and genotype specific differences in inflammation and degeneration of the substantia-nigral dopamine system in a multi-hit model of Parkinson's disease

Authors: ***S. BELLEVUE**, Z. DWYER, C. RUDYK, M. CHAIQUIN, S. HAYLEY; Carleton Univ., Ottawa, ON, Canada

Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting more that 1% of the population over the age of 60. PD is characterized by the progressive loss of dopamine (DA) producing neurons in the substantia nigra pars compacta (SNc). This results in motor deficits such as bradykinesia, altered gait and trembling, as well as other non-motor symptoms. According to the multi-hit hypothesis, PD is precipitated by exposure to an array of risk factors, including environmental toxins, inflammatory insults, and genetic vulnerabilities over many years. Interestingly, males display increased rates of incidence and severity of PD symptoms. The objective of our current research is to assess sex and genotype specific differences in inflammation and neurodegeneration using a multi-hit PD mouse model. To achieve this, both male and female adult wild-type mice and adult mice containing the G2019S mutation in the leucine-rich-repeat kinase 2 (LRRK2) gene, the most common genetic anomaly found in PD patients, were exposed to inflammatory insult, lipopolysaccharide (LPS) and environmental toxin, paraquat (PQ). Specifically, animals were primed with a single peripheral LPS treatment, followed by six peripheral treatments with PQ spanned over 21 days. During this time, motor behaviours were assessed using catwalk, rotarod, and micromax apparatuses. DA degeneration and inflammation in the SNc, and blood-brain-barrier permeability were assessed using immunohistological assays. It was found that the LPS-PQ challenge caused sex and genotype specific degeneration and inflammation of the SNc-DA system, and disruptions in blood-brain-barrier permeability. Moreover, this disruption was accompanied by deficits in motor behaviour. These findings uniquely characterize the role sex and the G2019S-

LRRK2 mutation plays in PD pathology and further supports the multiple-hit model of PD etiology.

Disclosures: **S. Bellevue:** None. **Z. Dwyer:** None. **C. Rudyk:** None. **M. Chaiquin:** None. **S. Hayley:** None.

Poster

762. Parkinson's Disease: Rodent Models III

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 762.15/B90

Topic: C.03. Parkinson's Disease

Title: Loss of striatal cholinergic interneurons in a transgenic synucleinopathy model leads to motor dysfunctions and induces adaptive changes in dopamine receptor levels

Authors: ***S. FRAHM**[1,2], K. SCHWAB[1,2], M. MAGBAGBEOLU[1,2], H. LÜCK[1,2], V. MELIS[3,2], G. RIEDEL[3], C. WISCHIK[2,3], C. R. HARRINGTON[2,3], F. THEURING[2,1];
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Abstract: Cholinergic interneurons have been implicated as key players in the pathogenesis of movement disorders. In synucleinopathies, the accumulation and aggregation of the alpha-synuclein protein in neurons of the basal ganglia network is critical for disease progression. Here we describe a mouse model overexpressing human wild-type alpha-synuclein in a subpopulation of striatal cholinergic interneurons that display bradykinesia and increased stereotypic behavior. We observed a 25% decrease in the number of cholinergic interneurons in the striatum and a concomitant reduction of ChAT expression in transgenic mice, but normal levels of extracellular dopamine, dopamine metabolites and synthesizing enzymes. Furthermore, remaining ChAT-positive interneurons that co-expressed alpha-synuclein showed a markedly reduced cell diameter compared to unaffected ChAT neurons. The resulting disruption of the striatal acetylcholine/dopamine balance in favor of dopamine induced an adaptive downregulation of D1 and D2 receptors (D1R and D2R), as well as upregulation of the muscarinic acetylcholine receptor M4 in transgenic mice, as shown in behavioral pharmacology and biochemical experiments. Interestingly, stereotypic movements induced by the D2R antagonist haloperidol were less pronounced and the anxiolytic effect of D1R agonists SKF81297 and apomorphine was completely reversed in transgenic animals, underlining the specificity of receptor subtypes and circuits involved in these behaviors. We conclude that pathological alpha-synuclein expression in cholinergic interneurons is sufficient to induce motor dysfunction and disruption of basal ganglia

synaptic integration through adaptive changes in receptor expression. Thus, our transgenic mice provide a useful model to test new therapeutic strategies for the treatment of synucleinopathies.

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Poster

762. Parkinson's Disease: Rodent Models III

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 762.16/B91

Topic: C.03. Parkinson's Disease

Title: Exogenous induction of α-synucleinopathy is governed by agent and host

Authors: *M. BACIOGLU[1], M. SCHWEIGHAUSER[2], J. MAHLER[2], B. M. WEGENAST-BRAUN[2], K. P. R. NILSSON[4], H. SCHELL[3], D. R. SHIMSHEK[5], P. J. KAHLE[3], Y. S. EISELE[2], M. JUCKER[2];
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Abstract: Aggregation of misfolded proteins is a common feature of many neurodegenerative diseases (Jucker & Walker, Nature, 2013). Parkinson's disease (PD) is characterized by intracellular deposits of aggregated α-synuclein in the form of Lewy bodies and Lewy neurites, which appear in a stereotypical manner in the brains of PD patients (Goedert et al, Nature Reviews Neurology, 2013). The mechanism underlying the formation and spreading of α-synuclein pathology is still puzzling. Inoculation studies, where α-synuclein lesions are induced in susceptible hosts, suggest that α-synuclein behaves in a prion-like protein by templated misfolding of soluble α-synuclein into insoluble aggregates (Luk et al, PNAS, 2009). In the first part of our study we aimed to further characterize this phenomenon using different α-synuclein transgenic (tg) mouse lines that all develop α-synuclein lesions with aging followed by premature death. We found that α-synuclein aggregates among the lines are not only morphologically different but also exhibit differential proteinase K sensitivities. Furthermore, by using conformation-sensitive dyes, distinct morphological properties of α-synuclein aggregates in the various mouse lines were found. To further investigate these findings, we inoculated tg

hosts with brain-derived extracts from terminally ill tg donors. We found an acceleration of end-stage α-synucleinopathy with a significantly reduced life span. In summary, we show that the α-synuclein protein exhibits strain-like features and a cell-to-cell propagation reminiscent of prions. However, more studies appear necessary to characterize these different aggregates and how they might affect disease onset and propagation.

Disclosures: **M. Bacioglu:** None. **M. Schweighauser:** None. **J. Mahler:** None. **B.M. Wegenast-Braun:** None. **K.P.R. Nilsson:** None. **H. Schell:** None. **D.R. Shimshek:** None. **P.J. Kahle:** None. **Y.S. Eisele:** None. **M. Jucker:** None.

Poster

762. Parkinson's Disease: Rodent Models III

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Topic: C.03. Parkinson’s Disease

Support: Ottawa Parkinson Research Consortium (PRC)

CIHR

Title: LRRK2 plays a role in substantia nigra dopaminergic cell loss in an environmental toxin model of Parkinson's disease

Authors: ***C. A. RUDYK**, Z. DWYER, S. E. BELLEVUE, S. P. HAYLEY;
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Abstract: Parkinson’s disease (PD) is a chronic progressive neurodegenerative disorder characterized by the presence of motor and non-motor behavioural deficits. Much attention has focused on the commonly used pesticide, paraquat (PQ), as an environmental risk factor for the development of PD. Animal models using PQ have been shown to recapitulate many of the hallmark pathological features of the disease. Additionally, neuroinflammatory and oxidative processes are critically important for PQ-induced degeneration of the substantia nigra pars compacta (SNc) dopamine (DA) neurons. Indeed, priming SNc neurons with the inflammatory agent, lipopolysaccharide (LPS), influences the impact of later exposure to the pesticide. The leucine-rich repeat kinase 2 (LRRK2), a kinase mutated in both inherited and sporadic PD cases, has been shown to modulate neuroinflammatory processes. Findings demonstrate that LRRK2 regulates neuroinflammation and its ablation attenuates the microglia proinflammatory response. However, whether or not LRRK2 plays a role in LPS primed PQ-induced brain and behavioral

changes has not yet been characterized. Accordingly, we investigated the effect of LPS-PQ exposure in male LRRK2 knockout (KO) and wild-type (WT) mice on motor, degenerative, and inflammatory outcomes. Results showed that LPS infusion into the SNc sensitized DA neurons to the neurodegenerative effects of a series of paraquat injections commencing 2 days later as well as increased microglial response in WT but not KO mice. Moreover, these alterations were accompanied by motor behavioural disturbances. These findings suggest that LRRK2 is critically involved in PQ induced inflammatory cascades induced by LPS-PQ exposure.

Disclosures: **C.A. Rudyk:** None. **Z. Dwyer:** None. **S.E. Bellevue:** None. **S.P. Hayley:** None.

Poster

762. Parkinson's Disease: Rodent Models III

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: C.03. Parkinson’s Disease

Support: NMRC-EDG (LKL)

Title: Exploiting the relationship between parkin and DMT1 to generate a novel "gene-environmental" mouse model of Parkinson's disease

Authors: ***B. H. CHAI**[1], C. ZHANG[1], A. Y. K. TAI[2], E. T. E. HONG[1], T. SOONG[2], K. LIM[1,2,3];
[1]Res., Natl. Neurosci. Inst., Singapore, Singapore; [2]Dept. of Physiol., Natl. Univ. of Singapore, Singapore, Singapore; [3]Duke-NUS Grad. Med. Sch., Singapore, Singapore

Abstract: Parkinson disease (PD) is a prevalent neurodegenerative disorder characterized by motor deficit as a consequence of damage to the nigrostriatal dopaminergic pathway. The disease remains incurable and the lack of a representative preclinical animal model has hampered efforts for drug discovery. Although the etiology of PD is unclear, exposure to divalent metals such as iron and manganese has consistently been implicated by epidemiological studies to be a significant risk factor for the disease. Under normal circumstances, cellular iron and manganese uptake is regulated by the Divalent Metal Transporter 1 (DMT1). Accordingly, alterations in DMT1 levels may underlie the abnormal accumulation of metal ions and thereby disease pathogenesis. Indeed, DMT1 expression has been demonstrated to be significantly elevated in the *substantia nigra* of PD patients compared to age-matched controls. Interestingly, parkin, a ubiquitin ligase associated with recessive parkinsonism, has separately been demonstrated to protect against metal-induced toxicity. Consistent with this, we found that the expression of

parkin is markedly enhanced in transgenic mice over-expressing DMT1, which likely explains their lack of observable phenotype. Accordingly, we have generated here a novel PD mouse model based on the transgenic overexpression of DMT1 against a parkin null background. Surprisingly, the double mutant mice display no significant nigrostriatal dopaminergic loss or overt locomotion defects in the absence or presence of long-term iron or manganese-enriched diet (fed over a period of 9-12 months) relative to control mice. However, these mutant mice do exhibit greater susceptibility towards 6-hydroxydopamine-induced dopaminergic neurotoxicty, and display enhanced rotational deficits following apomorphine administration as a result. Together, these findings suggests that multiple hits are required for the pathogenesis of PD to occur, which may help explain the lack of robust parkinsonism in virtually all the genetic mouse models of PD generated thus far.

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Poster

762. Parkinson's Disease: Rodent Models III

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Topic: C.03. Parkinson’s Disease

Support: NIH Grant NS060885

PAR fore Parkinson

National Parkinson Foundation CSRA

Title: Progressive age-dependent loss of nigrostriatal dopaminergic neurons in Progranulin deficient mice

Authors: R. BANERJEE[1,2], N. AMMAL KAIDERY[3], M. AHUJA[3], L. YANG[4], N. STARKOVA[5], A. DING[6], J. MORGAN[7], F. BEAL[5], A. STARKOV[5], *B. THOMAS[8]; [1]Lab. of Clin. & Exptl. Neurosci., CSIR-Indian Inst. of Chem. Biol., Kolkata, India; [2]Parkinson's Dis. and Movement Disorders Program, Inst. of Neurosciences, Kolkata, India; [3]Pharmacol. & Toxicology and Neurol., Georgia Regents Univ., Augusta, GA; [4]Kunmig Biomed, Hunan, China; [5]Neurol., [6]Microbiology and Immunol., Weill Med. Col. of Cornell Univ., New York, NY; [7]Neurol., Med. Col. of Georgia, Georgia Regents Univ., Augusta, GA; [8]Pharmacol. & Toxicology and Neurol., Med. Col. of Georgia, Georgia Regents Univer, Augusta, GA

Abstract: Loss-of-function mutations in the progranulin (PGRN) gene have been causally associated with a significant number of neurodegenerative diseases including frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD) and Parkinson's disease (PD). An insufficient level of PGRN leading to unrestrained inflammation is thought to contribute, in part, to the pathogenesis of these diseases. Whether dysregulated PGRN expression underlies the pathogenesis of PD and contributes to the loss of nigrostriatal dopaminergic neurons is as yet, unknown. Here we show that PGRN is expressed by midbrain dopaminergic neurons in mice and humans. Compared to the wild type mice PGRN deficient mice showed progressive age-dependent loss of nigrostriatal dopaminergic neurons as assessed by stereological cell counts of tyrosine hydroxylase and Nissl positive neurons in substantia nigra. In addition, PGRN-deficient mice showed augmented age-dependent accumulation of ubiquitin, alpha-synuclein, and TAR DNA binding protein-43, as well as activation of microglia and astrocytes in the substantia nigra. These neuropathological changes were associated with increased production of pro-inflammatory cytokines and chemokines but not mitochondrial dysfunction in the ventral midbrain of aged PGRN-deficient mice. Our data suggest that PGRN-deficiency could lead to the development of PD associated neuropathology due to exaggerated inflammation and aging. Therapeutic strategies to induce PGRN expression could serve as a promising approach to block neurodegeneration in PD.

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Poster

762. Parkinson's Disease: Rodent Models III

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Support: FAPESP

CNPq

CAPES

NAPNA

USP

Title: Cannabinoids compounds attenuate sensorimotor gating disruption induced by amphetamine in mice

Authors: *A. DE CASTRO ISSY PEREIRA[1], J. CORDEIRO PEDRAZZI[2], F. VILLELA GOMES[3], F. SILVEIRA GUIMARÃES[3], E. DEL-BEL[4];
[2]Behavioral Neurosci. (FMRP), [3]Pharmacol. (FMRP), [4]Physiol. (MFPB-FORP), [1]Univ. of Sao Paulo, Ribeirão Preto, Brazil

Abstract: Introduction. Schizophrenia is a highly disabling disease, which would involve an imbalance in the dopaminergic neurotransmission and a glutamatergic hypofunction. The information processing appears to be deficient in schizophrenia. Prepulse inhibition (PPI), which measures the inhibition of a motor response by a weak sensory event, is considered particularly useful to understand the biology of information processing in schizophrenia patients. Drugs that facilitate dopaminergic neurotransmission such as amphetamine induce PPI disruption in human and rodents. Clinical and neurobiological findings suggest that the endocannabinoid system and cannabinoids may be implicated in the pathophysiology and treatment of schizophrenia. Cannabidiol (CBD), a non-psychotomimetic constituent of the Cannabis sativa plant, has also been reported to have potential as an antipsychotic. Objective. Our aim was to investigate if CBD pretreatment was able to prevent PPI disruption induced by amphetamine. Since one possible mechanism of CBD action is the facilitation of endocannabinoid mediated neurotransmission through anandamide, we tested the effects of an anandamide hydrolysis inhibitor (URB597) in the amphetamine induced PPI disruption. Methods. Male Swiss mice were treated with CBD systemic or intra-accumbens, or URB597 (systemic) prior to amphetamine and were exposed to PPI test. The PPI test consist of 64 trials irregularly divided into pulse (P, white noise, 105 dB), prepulse (PP; pure tone; 7kHz; 80, 85 or 90 dB), prepulse + pulse (PP+P) and no-stimuli with white background noise level of 64 dB - %PPI=[100-(PP+P/P)*100]. The PPI results were analyzed by mixed-design ANOVA with treatments (treatment 1, vehicle or CBD; treatment 2, saline or amphetamine) as the main independent factors, and prepulse intensity (80, 85, and 90 dB) as the repeated factor. Data from URB597 were analyzed by repeated measures with treatment as between-subject factors and prepulse intensity as a within subject factor. Duncan´s post hoc test ($p<0.05$) was used to specify differences. Results. Amphetamine (10 mg/kg) disrupted PPI while CBD (15-60 mg/kg) or URB597 (0.1-1 mg/kg) administered alone had no effect. Pretreatment with CBD attenuated the amphetamine disruptive effects on PPI test after systemic or intra-accumbens administration. Similar effects were also found with the inhibitor of anandamide hydrolysis. Conclusion. These results corroborate findings indicating that CBD induces antipsychotic like effects. In addition, they pointed to the nucleus accumbens as a possible site of these effects. The increase of anandamide availability may be enrolled in the CBD effects.

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Poster

762. Parkinson's Disease: Rodent Models III

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Topic: C.03. Parkinson’s Disease

Support: CNPq

FAPESP

CAPES

Title: Nitric oxide modulation effects in the reserpine-induced oral abnormal involuntary movements in rats

Authors: *M. BORTOLANZA, A. ISSY, K. BARIOTTO, C. A. DA-SILVA, E. A. DEL-BEL; Univ. of São Paulo, Ribeirão Preto, Brazil

Abstract: In patients with Parkinson’s disease L-DOPA-induced abnormal involuntary movement (dyskinesia) is an inevitable complication associated with long-term treatment. Rodents treated with reserpine develop spontaneous oral dyskinesia, usually described as vacuous chewing movements (VCM) and tongue protrusion (TP). In contrast to L-DOPA induced dyskinesia reserpine-induced oral dyskinesia develops rapidly reaching a maximal level within 3 days at a dose of 1 mg/kg per day. They are different with respect to the underlying disease, but they both share similarities. It is believed that a deregulation occurs at striatal dopaminergic receptors or related to non-dopaminergic neurotransmitters systems playing a role in the development and persistence of the mechanisms causing dyskinesia. Our group described that L-DOPA-induced dyskinesia in hemiparkinsonian rodents could be attenuated with nitric oxide synthase inhibitors. The aim of this study was to extend our findings to another experimental condition of pharmacologically induced oral dyskinesia. Thus, the present study investigated the nitric oxide system modulation on oral dyskinesia induced by reserpine. Male Wistar rats received either vehicle or reserpine (1mg/kg/day, s.c.) during two days, with 24h of interval, preceded by saline or the nitric oxide inhibitor NG-nitro-l-arginine-methyl ester (L-NAME; 10 or 50mg/kg/day, i.p.), or the nitric oxide donor sodium nitroprusside (SNP; 2 or 4mg/kg/day, i.p.). Rats were placed individually in glass cages containing a mirror at the wall to permit the evaluation of the VCM and TP. Animals were recorded during 5 min, after 1 min habituation. Data were analyzed with one-way ANOVA. Duncan´s post hoc test ($p<0.05$) was used to specify individual effects. Reserpine treatment elicits an increased number of abnormal involuntary oral movements in rats and reduced the locomotor activity. L-NAME at two different

doses significantly reduced reserpine-induced oral movements. SNP treatment showed no significant effects. These results corroborate and extend findings indicating that nitric oxide inhibitors are able to attenuate the pharmacological induced oral dyskinesia. This approach may allow the use of a simple rodent model to provide an initial assessment of whether potential adjunctive therapies to L-DOPA might have actions to reduce motor complications associated with L-DOPA therapy (dyskinesia). Given the simplicity of this model, acute systemic drug administration, compared with other models of dyskinesia (repeated L-DOPA-treatment in the 6-OHDA-lesioned rat) a potential utility in providing an initial indication of therapeutic benefit is great.

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Poster

762. Parkinson's Disease: Rodent Models III

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Program#/Poster#: 762.22/B97

Topic: C.03. Parkinson's Disease

Title: Cannabidiol modulates L-DOPA induced dyskinesia via CB1 receptor

Authors: *M. S. PEREIRA[1], C. SILVA[2], F. GUIMARÃES[3], E. DEL BEL[2];
[2]FORP, [3]FMRP, [1]Univ. De São Paulo, Ribeirão Preto, Brazil

Abstract: The cannabinoid system is emerging as an important modulator of basal ganglia functions. Pharmacologic manipulation of this system represents a promising therapy to alleviate L-DOPA-induced dyskinesias (LID). Our aim is to verify if the major non-psychoactive cannabis constituent cannabidiol (CBD) modulates LID in hemiparkinsonian mice. C57BL/6 mice with a striatal 6-hydroxydopamine-induced lesion received L-DOPA (25 mg/kg + benserazide 10 mg/kg i.p.) for 21 days and develop dyskinesia characterized by axial, limb, locomotor and orofacial abnormal involuntary movements (AIMS). After that, mice received CBD (15, 30 or 60 mg/kg i.p.) 30 minutes prior to L-DOPA for 3 days. To analyze a possible involvement of the transient receptor potential vanilloid 1 receptors (TRPV-1) in CBD effects, the TRPV-1 antagonist capsazepine (1 or 5 mg/kg; 45 minutes prior to L-DOPA) was administered in association with CBD (30 mg/kg) or vehicle. We also treated animals with arachdonoyl-serotonin (AA5HT; 5 mg/kg i.p., 30 minutes prior to L-DOPA), an inhibitor of the fatty acid amide hydrolase (FAAH) and potent TRPV-1 blocker, in the hemiparkinsonian mice. For dyskinesia analysis, mice were videotaped and scored based on the protocol described by Pavon et al. (2006). CBD *per se* did

not influence axial, limbic and orofacial or locomotor AIMs in any of the doses (AIMS: CBD15: 30.38 ± 6.31 vs. 27.81 ± 6.40; CBD30: 34.63 ± 4,82 vs. 29.75 ± 5.13; CBD60: 34.63 ± 4.82 vs. 33.25 ± 6.40, $p > .05$); Locomotor: CBD 15: 2.56 ± 1.09 vs. 1.31 ± 0.60; CBD 30: 1.81 ± 0.72 vs. 0.93 ± 0.39; CBD 60: 1.91 ± 0.82 vs. 1.93 ± 0.67, $p > .05$). Capsazepine also did not reduce axial, limbic and orofacial AIMs at the dose of 1 mg/kg (34.56 ± 5.33 vs. 36.94 ± 5.68; $p > .05$) or 5 mg/kg (33.31 ± 5.89 vs. 28.63 ± 5.40, $p > .05$), as it was unable to change the locomotor AIMs (1mg: 1.37 ± 0.41 vs. 2.62 ± 0.52; 5mg: 1.62 ± 0.47 vs. 1.00 ± 0.43, $p > 0.05$). However, capsazepine associated with CBD significantly reduced axial, limbic and orofacial AIMs at both doses (1mg + CBD = 34.56 ± 5.33 vs. 15.88 ± 5.16; 5mg + CBD =33.31 ± 5.89 vs. 15.69 ± 5.70, $p < .01$) without altering locomotor AIMs (1g + CBD: 1.37 ± 0.41 vs. 0.87 ± 0.30; 5mg + CBD: 1.62 ± 0.47 vs. 0.81 ± 0.32, $p > .05$). Similarly, AA5HT significantly decreased axial, limbic and orofacial AIMs (31.88 ± 5.72 vs. 19.13 ± 5.26, $p < .01$) but did not alter locomotor AIMs (1.25 ± 0.48 vs. 1.56 ± 0.31, $p > .05$). Our data indicates that CBD when associated with CPZ decreases the manifestations of LID. Since CBD inhibits FAAH but activates TRPV1 receptors, our results, together with the effects of AA5HT, suggest that CB1 activation by anandamide associated with the blockade of TRPV-1 can be a possible treatment for L-DOPA-induced dyskinesia.

Disclosures: **M.S. Pereira:** None. **C. Silva:** None. **F. Guimarães:** None. **E. Del Bel:** None.

Poster

762. Parkinson's Disease: Rodent Models III

Location: Hall A

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Topic: C.03. Parkinson’s Disease

Support: Inserm

ANR grant 13 SAMA001401 (to SC)

Fondation NeuroDis

Association France Parkinson

Région Rhône-Alpes (ARC 2)

Title: Role of dorsostriatal D3 receptors in motivational processes: implication for neuropsychiatric symptoms in Parkinson’s disease

Authors: M. FAVIER, C. CARCENAC, G. DRUI, S. BOULET, M. SAVASTA, *S. CARNICELLA;
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Abstract: We recently developed a rodent model reproducing the major motivational and affective impairments described in Parkinson's disease (PD), by using partial and bilateral 6-hydroxydopamine (6-OHDA) lesions of the substantia nigra pars compacta (SNc) (Drui et al., Mol Psychiatry, 2014). We further showed that the motivational deficits related to PD neuropsychiatric symptoms, observed in SNc-lesioned animals, can be fully reversed by specific activation of dopaminergic (DA) D3 receptors (D3R) (Carnicella et al., Transl Psychiatry, 2014). In the present study, using quantitative autoradiography, we demonstrated that D3R are specifically down-regulated in the dorsal striatum of 6-OHDA-lesioned rats. By combining intracerebral infusion of a selective D3R (SB-277011A) or D2R (L-741,626) antagonist into the dorsal striatum of non-lesioned animals with the use of instrumental and non-instrumental behavioral tasks, we showed next that blockade of D3R, but not D2R neurotransmission reproduce the motivational impairments seen in our lesion-based model. Moreover, we observed that the behavioral deficits related to dorsostriatal D3R inhibition was specifically implicated in the maintenance of instrumental behaviors. Interestingly, infusion of SB-277011A into the nucleus accumbens also modified the motivational state of the animals, but this effect was rather linked to deficits in the invigoration of reward-seeking behaviors. Our findings unravel an unsuspected involvement of dorsostriatal D3R in motivational processes and suggest complementary psychobiological roles of D3R in dorsal and ventral striatum. In addition, this study strengthens the idea that targeting D3R neurotransmission may be a valuable strategy for the treatment of PD-related neuropsychiatric symptoms.

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Poster

762. Parkinson's Disease: Rodent Models III

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 762.24/B99

Topic: C.03. Parkinson's Disease

Support: DFG clinical research group KFO219

Title: Functional connectivity changes following deep brain stimulation in the subthalamic nucleus measured with FDG-PET

Authors: E. KORDYS[1], N. APETZ[2], F. JUNG[2], B. NEUMAIER[1], A. DRZEZGA[3], L. TIMMERMANN[2], *H. ENDEPOLS[1];
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Abstract: Deep brain stimulation in the subthalamic nucleus (DBS-STN) is a successful therapeutic approach to treat motor symptoms of Parkinson's disease. Because functional network changes underlying DBS-STN are not fully understood, we combined DBS-STN with functional [18F]FDG-PET in a rat hemiparkinson model. Parkinson-like symptoms were induced by injecting 6-hydroxydopamine (6-OHDA) unilaterally into the medial forebrain bundle. Automated gait analysis and [18F]FDOPA-PET confirmed motor impact and dopaminergic lesion, respectively. For DBS-STN an electrode was inserted through a chronically implanted guide cannula aiming at the ipsilesional STN. Two weeks after 6-OHDA injection, [18F]FDG (2 mCi) was injected intraperitoneally, and immediately after injection awake and freely moving rats (n=5) underwent one of three randomized stimulation conditions for 40 minutes: 1) DBS-STN with a pulse rate of 130 Hz. 2) OFF-stimulation. 3) Without electrode (control). 60 min after FDG injection, animals were anesthetized and a brain scan was acquired in a small animal PET scanner (Focus 220, Siemens). This procedure was repeated with the other stimulation conditions on different days. Ipsilesional DBS-STN increased metabolic activity compared to control in the ipsilateral striatum and septum in all animals. During OFF-stimulation contralateral hippocampal activity was lower than during control, indicating a mechanical effect of the electrode. Depending on the exact electrode location, FDG uptake increased during DBS-STN in the ipsilateral SNr, amygdala, piriform cortex, and ventral subiculum. Intra-individual difference images (DBS-STN minus OFF-stimulation) were used for a seed-based correlative analysis. The seed placed in the ipsilateral striatum revealed functional connections during stimulation to motor-related areas including the contralateral striatum, globus pallidus, M1, and cerebellum. Our study shows that DBS-STN changes functional connectivity in the basal ganglia network, particularly within key areas related to pathologic motor symptoms in a rat model of Parkinson's disease.

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Poster

762. Parkinson's Disease: Rodent Models III

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Support: IRHPA, Department of Science and Technology, Govt. of India

J.C. Bose National fellowship to VR

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Title: A novel mouse model of Parkinson's disease: Diamide, a potent thiol oxidant, causes degeneration of dopaminergic neurons and Parkinsonism phenotype in mice

Authors: *A. RAY, M. KAMBALI, V. RAVINDRANATH;
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Abstract: Single unilateral administration of diamide, a potent thiol oxidant, into substantia nigra (SN) of mice leads to emergence of locomotor deficits and degeneration of dopaminergic neurons in the SN pars compacta (SNpc). Diamide-injected mice showed hemiparkinsonian behavior, measured as spontaneous contralateral rotations, poor grip strength and impaired locomotion on rotarod. Tyrosine hydroxylase immunostaining revealed significant loss of dopaminergic neurons in SNpc and their striatal fibers in the ipsilateral but not contralateral sides. We also saw an increase in Fluoro-Jade C labeling and loss of NeuN staining, indicative of neurodegeneration. Importantly, diamide injection led to ipsilateral aggregation of α-synuclein in SNpc neurons, a hallmark of PD pathology, not often discerned in animal models of PD. Upon investigating putative mechanism(s) involved in the degenerative process, we observed loss of the major non-protein thiol glutathione, which is essential for maintaining protein thiol homeostasis. Concomitant with loss of glutathione, we observed activation of the redox-sensitive ASK1-p38 MAPK death signaling pathway in ipsilateral but not contralateral ventral midbrain. In Neuro-2a cells, diamide activated ASK1-p38 cascade through oxidation of the thiol disulfide oxidoreductase thioredoxin 1, leading to cell death, which was abolished by ASK1 knockdown. Since diamide selectively disrupts protein thiol homeostasis, we can now attempt to understand the molecular determinants of the selective vulnerability of dopaminergic neurons to such perturbations. Identifying the precise role of dysregulation of protein thiol homeostasis in neurodegeneration, especially early in disease, will not only facilitate identification of death signaling cascades, but potentially aid in developing disease-modifying strategies for PD.

Disclosures: A. Ray: None. **M. Kambali:** None. **V. Ravindranath:** None.

Poster

762. Parkinson's Disease: Rodent Models III

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Topic: C.03. Parkinson's Disease

Support: Fondation de France_Physiopathologie de la maladie de Parkinson

Fédération Française des Groupement de Parkinsonien_Sponsoring

Title: Levodopa chronic treatment promotes reinforcing properties of pramipexole in an alpha-synuclein rat model of Parkinson's disease: linking behavior to transcriptional modifications

Authors: *S. LOIODICE[1,2], P. WINLOW[2], S. DREMIER[2], A. HAFIDI[1], A. NOGUIERA DA COSTA[2], F. DURIF[1];
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Abstract: Parkinson Disease (PD) is characterized by a progressive dopaminergic (DA) cell loss in the Substantia Nigra pars compacta (SNc) inducing motor disorders which can be reversed by DA replacement therapies (DRT). About 10% of patients develop medication overuse, a disorder called dopamine dysregulation syndrome (DDS). Based on similarities between DA hypersensitization in drug addiction and PD, we hypothesized that DDS is due to a synergic effect of nigrostriatal lesion and repeated administration of DRT. Our objective is to specify the physiopathology of this addictive disorder. We performed a bilateral lesion of the SNc in rat (n=96) using an AAV-mediated strategy enabling the overexpression of the a-synuclein (a-syn) protein. Five weeks after surgery, animals were chronically treated with L-Dopa/benserazide during 3 weeks. Motor assessment was performed on week 8 by a rotarod test. Reinforcing properties of pramipexole (ppx) were assessed using a conditioned place preference (CPP) test. Brains were sampled for immunohistochemistry, microarray (genome-wide expression) and qPCR analysis. A-syn overexpression induced a SNc lesion (about 70% of DA cell loss) accompanied by significant motor coordination impairment that was reversed by L-dopa. Repeated administration of L-Dopa enhanced the reinforcing properties of ppx in the CPP test (1.4 fold increase of time spent in drug paired side after conditioning). This enhancement was increased when animals were SNc-lesioned (1.6 fold increase of time spent in drug paired side after conditioning) indicating that PD context and chronic DA stimulation may promote the reinforcing properties of ppx in a synergistic manner. Moreover, the molecular analysis highlighted a panel of 7 genes that were significantly modulated. With qPCR analysis, we confirmed an increase in expression of Oxt (associated to modulation of the DA pathway) in dorsal striatum of SNc lesioned animals receiving L-dopa. We also revealed that L-dopa induced expression of Egr2 and Grm5 (within lesioned animals). These results suggest that expression of the ppx rewarding properties could have been promoted by neuroplasticity events already described in dyskinesia and drug abuse contexts. The results obtained suggest that DDS is not only a side effect of DRT. It may be considered that DA hypersensitization related to PD is increased by repeated DA stimulation. To the best of our knowledge, this is the first study where

a transcriptional profile of DDS emphasizes the role of a neuroplasticity phenomenon associated to DDS and suggesting that over medication of DRT in PD occurs in a specific sensitized context.

Disclosures: **S. Loiodice:** None. **P. Winlow:** A. Employment/Salary (full or part-time):; UCB Biopharma sprl. **S. Dremier:** A. Employment/Salary (full or part-time):; UCB Biopharma sprl. **A. Hafidi:** None. **A. Noguiera da Costa:** A. Employment/Salary (full or part-time):; UCB Biopharma sprl. **F. Durif:** None.

Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: C.03. Parkinson’s Disease

Support: NS089544

NS060872

Title: Hdac6 mediates the action of Parkinson's disease-related lrrk2 mutations

Authors: ***C. B. TRENGROVE**[1], H. LI[3], J. DUSONCHET[4], J. Y. BOON[2], M. GUILLILY[2], M. LIU[5], A. MAMAIS[6], A. CITRO[2], K. YOUMANS[2], Z. YUE[7], R. BANDOPADHYAY[6], M. A. GLICKSMAN[5], J. J. COLLINS[8], B. WOLOZIN[2];
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Abstract: LRRK2 is a large cytoplasmic protein linked to an autosomal dominant form of Parkinson’s disease (PD). It contains multiple functional domains, including a kinase and GTPase domain, but the mechanism by which these mutations lead to disease remain unclear. Studies increasingly highlight the importance of autophagy in the biology of PD. Here we show that LRRK2 and its disease-associated mutations form a complex with HDAC6, a histone deacetylase known to regulate quality control autophagy (1). We further show that

phosphorylation of HDAC6 is enhanced in brains from patients with sporadic PD. We pursued this putative link further, and show that LRRK2 and its mutations stimulate tubulin deacetylation. Given the strong involvement of HDAC6 with autophagy and its tight regulation with LRRK2, we investigated whether LRRK2 regulates autophagy through this interaction with HDAC6. RNAi experiments reveal that LRRK2 harboring disease-associated mutations exhibits increased dependence on HDAC6 for regulation of autophagy. Similarly, overexpression experiments reveal the same close regulation of HDAC6 with the LRRK2 mutants. HDAC6 was also able to rescue neurite retraction in G2019S transfected SH-SY5Ys. These studies identify a key role for HDAC6 in LRRK2 biology. Disease linked LRRK2 mutations reduce the ability of LRRK2 to stimulate autophagic flux. These results highlight a novel mechanism for regulation of mutant LRRK2 deficits through HDAC6, and identify a pathway by which mutations in LRRK2 could mediate Parkinson's disease.

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Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: C.03. Parkinson's Disease

Support: The Michael J. Fox Foundation for Parkinson's Research

Title: LRRK2 kinase inhibitors of different structural classes induce abnormal, but reversible, accumulation of lamellar bodies in type II pneumocytes in non-human primates

Authors: *M. A. BAPTISTA[1], K. M. MERCHANT[1], S. BHARGHAVA[2], D. BRYCE[3], M. ELLIS[3], A. A. ESTRADA[4], M. FELL[3], R. N. FUJI[4], P. GALATSIS[2], S. HILL[3], W. D. HIRST[2], C. HOULE[2], M. KENNEDY[3], X. LIU[4], M. MADDESS[3], C. MARKGRAF[3], H. MEI[3], E. NEEDLE[2], S. STEYN[2], Z. YIN[3], H. YU[3], B. K. FISKE[1], T. B. SHERER[1];
[1]Michael J. Fox Fndn., New York, NY; [2]Pfizer, Cambridge, MA; [3]Merck and Co., Boston, MA; [4]Genentech Inc, South San Francisco, CA

Abstract: Leucine-rich repeat kinase 2 (LRRK2) mutations are the most common cause of genetic Parkinson's disease (PD), accounting for 1-2% of all cases and up to 40% in some ethnic

groups. Several mutations in LRRK2 increase kinase activity and have been shown to be neurotoxic, hence the interest in the discovery and development of drugs that inhibit the kinase activity of LRRK2 to slow the progression of PD. To this end, Fuji et al. (2015) recently undertook and reported the results of toxicology studies of two LRRK2 kinase inhibitors (GNE-7915 and GNE-0877) in non-human primates (NHPs). Abnormal accumulations of lamellar bodies in type II pneumocytes were seen with both inhibitors after 7- and/or 29 days of daily dosing. The present study was undertaken with two major aims: (a) to confirm that the lung effect was not chemotype-specific and therefore mediated by inhibition of LRRK2 kinase activity, by testing LRRK2 kinase inhibitors of very distinct structural classes (PFE-360 and MLi-2), and (b) to assess the reversibility of the lung finding by evaluating NHP lungs after 2 weeks off dosing of GNE-7915. PFE-360 and MLi-2 were administered to cohorts at two dose levels for two weeks. GNE-7915 was administered at one dose level for two weeks as positive control, with one cohort evaluated after a 2-week dose-free period. The low doses of PFE-360 and MLi-2 targeted kinase inhibition similar to that reported for the GNE-7915 dose, and the high doses targeted 10x kinase inhibition. All three LRRK2 kinase inhibitors reduced pSer935 in the lungs by >90% at all doses tested (at Cmax). However, the same mild type II pneumocyte change was only observed at the high doses of PFE-360 and MLi-2. GNE-7915 also induced the effect as expected; importantly, absence of the lung change was seen after two weeks off dosing. Overall, these data indicate that the lung pathology is an on-target effect of LRRK2 kinase inhibition, but reversible. Encouragingly, we also observed that it was possible to inhibit brain LRRK2 kinase activity with the lower doses of PFE-360 and MLi-2 without producing the lung effect. Currently, we are investigating whether the abnormal lung morphology is associated with pulmonary functional deficits as this information is essential in assessing respiratory system risk and in informing the monitoring of this potential lung safety liability in patients.

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Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

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Topic: C.03. Parkinson’s Disease

Support: The Michael J. Fox Foundation for Parkinson's Research

Title: Histological and clinical pathology in LRRK2-related mouse and rat models

Authors: *T. N. MARTINEZ[1], M. A. S. BAPTISTA[1], M. A. GREELEY[2], M. T. HERBERTH[2], D. KOVARIK[1], A. MARTIG[1], K. D. DAVE[1], M. A. FRASIER[1], B. FISKE[1], T. SHERER[1]; [1]Res. Programs, The Michael J. Fox Fndn. For Parkinson's Res., New York, NY; [2]WIL Res., Ashland, OH

Abstract: Several mutations in the gene leucine-rich repeat kinase 2 (LRRK2) are associated with autosomal-dominant late-onset Parkinson's disease (PD). The common G2019S mutation in the kinase domain increases LRRK2 kinase activity and may explain LRRK2-related PD pathology. Thus, inhibition of LRRK2 kinase activity is an attractive target for developing novel therapeutic approaches for PD patients. As part of a broad effort to determine the impact of loss of LRRK2 function, which may be concomitant to pharmacological inhibition of LRRK2 kinase activity, we undertook a rigorous study of histological and clinical pathology readouts in LRRK2-related mouse and rat models. We previously reported progressive kidney pathology (cytoplasmic vacuolation, hyaline droplets, and pigment accumulation) and mild lung pathology (observed only with advanced age and by electron microscopy analysis) associated with loss of LRRK2 in Long Evans rats at several ages (Baptista, M.A. et al., PLOS One, 2013). Here we summarize recent pathology findings in LRRK2-/- and LRRK2+/+ C57Bl/6 mice at several ages, LRRK2 gene dosage effects in LRRK2-/-, LRRK2+/- and LRRK2+/+ rats, and potential LRRK1 genetic interaction in LRRK1/2 double knockout versus wild type rats. The progressive kidney pathology findings in LRRK2-/- mice generally recapitulated previous observations in LRRK2-/- rat models albeit with some species differences, including an apparent earlier onset in mice compared to rats. In addition, lung pathology (cytoplasmic vacuolation in Type II pneumocytes) was more severe in LRRK2-/- mice than in LRRK2-/- rats and observable using light microscopy. In the rat studies, we observed evidence of a LRRK2 gene-dosage effect for kidney pathology and apparent exacerbation of LRRK2-related kidney pathology with loss of LRRK1. However, studies to examine potential LRRK2 gene dosage effects or LRRK1 interactions were not conducted in mice. These results may inform follow-up pathology and toxicology studies aimed at therapeutic strategies to modulate LRRK2 levels or kinase activity.

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Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

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Program#/Poster#: 763.04/B105

Topic: C.03. Parkinson's Disease

Title: *Ex vivo* inhibition of LRRK2 phosphorylation by a new kinase inhibitor in peripheral blood cells of subjects with and without G2019S LRRK2 mutation

Authors: *P. PLAS[1], C. ROUSSELIE[2], F. BONELLO[2], K. TAHIRI[2], S. ROLLAND[1], F. SCHMIDLIN[1], B. SPINNEWYN[1], C. TRANCHANT[3], M. ANHEIM[3], P. KRACK[4], A. CASTRIOTO[4], P. DAMIER[5], S. LE DILY[5], T. DANAILA[6], I. ROULLET-SOLIGNAC[6], V. CHAIGNEAU[7], O. RASCOL[7], S. FORLANI[2], A. BRICE[8], P.-E. CHABRIER[1], J.-C. CORVOL[2];
[1]IPSEN, Les Ulis, France; [2]Sorbonne Universités, UPMC Univ. Paris 06, INSERM UMRS_1127 and CIC_1422, CNRS UMR_7225, AP-HP, ICM, DNA and Cell Bank, CHU Pitié-Salpêtrière, Paris, France, Paris, France; [3]service de Neurologie Hop. de Hautepierre 1 Avenue Molière 67000 Strasbourg ; et Fédération de Médecine Translationnelle, Faculté de médecine , Strasbourg, Strasbourg, France; [4]Fonctions Cérébrales et Neuromodulation, Inst. des Neurosciences de Grenoble - Inserm U.836-UJF-CEA-CHU, Grenoble, France; [5]CHU de Nantes, INSERM CIC_0004, Nantes, France, Nantes, France; [6]Service de Neurologie, CHU de Lyon, Lyon, France, Lyon, France; [7]INSERM, NS-Park network and CIC_9302, CHU de Toulouse, Toulouse, France, Toulouse, France; [8]DNA and cell bank, ICM CNRS UMR 7225, Inserm U1127, UPMC-P6 UMRS 1127, Paris, France

Abstract: Parkinson's disease (PD) is a progressive disorder of the central nervous system leading to dopaminergic neuron loss. Although commonly sporadic, mutations in *PARK8*, encoding the Leucine-Rich Repeat Kinase 2 protein (LRRK2), have been associated with late onset autosomal dominant genetic forms of PD. The most common mutation of LRRK2, G2019S, leads to an increase in its kinase activity in transfected cells or transgenic knock-in mice. In cell cultures, this gain of function is directly related to neurotoxicity. LRRK2 is expressed in different tissues and notably in human peripheral blood mononuclear cells (hPBMC). Different sites of phosphorylation and autophosphorylation have been described including serine 935 (Ser935) which is correlated to the LRRK2 activity. We evaluated the effect of a new LRRK2 kinase inhibitor, ODS2005294 (IPSEN-ONCODESIGN compound), on LRRK2 phosphorylation on Ser935 after *ex vivo* incubation on fresh blood collected from PD patients with G2019S mutation (n = 11), and their first degree asymptomatic relatives carrying (n = 13) or not carrying (n = 10) the same mutation. Blood samples were collected in five centers in France and immediately incubated with ODS2005294 during 1h at 30µM (equivalent to 180 nM of free compound). Signals of pSer935-LRRK2 and LRRK2 were measured on hPBMC lysates by using a Homogeneous Time Resolved Fluorescence (HTRF) immunoassay. This technology based on a transfer of energy between two fluorophores fixed on antibodies was specifically

developed for this study and compared to western blots. Our data show a significant 64% (p value <0.001) decrease in pSer935-LRRK2 and 58% (p value < 0.001) for the ratio pSer935-LRRK2/LRRK2 in PBMCs for patients and relatives after LRRK2 inhibitor exposure as compared to vehicle. Similar results were found in parallel by Western blot. Altogether, we showed that ODS2005294 is able to inhibit the phosphorylation on the serine 935 of LRRK2 in hPMBC from subjects with PD with G2019S, as well as from their asymptomatic relatives with or without G2019S mutation. We were able to monitor this effect by a HTRF immunoassay suitable for a future use in clinical study.

Disclosures: **P. Plas:** A. Employment/Salary (full or part-time):; IPSEN, service de Neurologie Hopital de Hautepierre 1 Avenue Molière 67000 Strasbourg, Fonctions Cérébrales et Neuromodulation, Institut des Neurosciences de Grenoble - Inserm U.836-UJF-CEA-CHU, CHU de Nantes, INSERM CIC_0004, Nantes, France, Service de Neurologie, CHU de Lyon, Lyon, France, INSERM, NS-Park network and CIC_9302, CHU de Toulouse, Toulouse, France, DNA and cell bank, ICM CNRS UMR 7225, Inserm U1127, UPMC-P6 UMRS 1127. **C. Rousselie:** A. Employment/Salary (full or part-time):; Sorbonne Universités, UPMC Univ Paris 06, INSERM UMRS_1127 and CIC_1422, CNRS UMR_7225, AP-HP, ICM, DNA and Cell Bank, CHU Pitié-Salpêtrière, Paris, France. **F. Bonello:** A. Employment/Salary (full or part-time):; Sorbonne Universités, UPMC Univ Paris 06, INSERM UMRS_1127 and CIC_1422, CNRS UMR_7225, AP-HP, ICM, DNA and Cell Bank, CHU Pitié-Salpêtrière, Paris, France. **K. Tahiri:** A. Employment/Salary (full or part-time):; Sorbonne Universités, UPMC Univ Paris 06, INSERM UMRS_1127 and CIC_1422, CNRS UMR_7225, AP-HP, ICM, DNA and Cell Bank, CHU Pitié-Salpêtrière, Paris, France. **S. Rolland:** A. Employment/Salary (full or part-time):; IPSEN. **F. Schmidlin:** A. Employment/Salary (full or part-time):; IPSEN. **B. Spinnewyn:** A. Employment/Salary (full or part-time):; IPSEN. **C. Tranchant:** A. Employment/Salary (full or part-time):; service de Neurologie Hopital de Hautepierre 1 Avenue Molière 67000 Strasbourg ; et Fédération de Médecine Translationnelle, Faculté de médecine , Strasbourg. **M. Anheim:** A. Employment/Salary (full or part-time):; service de Neurologie Hopital de Hautepierre 1 Avenue Molière 67000 Strasbourg et Fédération de Médecine Translationnelle, Faculté de médecine , Strasbourg. **P. Krack:** A. Employment/Salary (full or part-time):; Fonctions Cérébrales et Neuromodulation, Institut des Neurosciences de Grenoble - Inserm U.836-UJF-CEA-CHU. **A. Castrioto:** A. Employment/Salary (full or part-time):; Fonctions Cérébrales et Neuromodulation Institut des Neurosciences de Grenoble - Inserm U.836-UJF-CEA-CHU. **P. Damier:** A. Employment/Salary (full or part-time):; CHU de Nantes, INSERM CIC_0004, Nantes, France. **S. Le Dily:** A. Employment/Salary (full or part-time):; CHU de Nantes, INSERM CIC_0004, Nantes, France. **T. Danaila:** A. Employment/Salary (full or part-time):; Service de Neurologie, CHU de Lyon, Lyon, France. **I. Roullet-Solignac:** A. Employment/Salary (full or part-time):; Service de Neurologie, CHU de Lyon, Lyon, France. **V. Chaigneau:** A. Employment/Salary (full or part-time):; INSERM, NS-Park network and CIC_9302, CHU de Toulouse, Toulouse, France. **O. Rascol:** A. Employment/Salary (full or part-time):; INSERM, NS-Park network and CIC_9302, CHU de Toulouse, Toulouse, Franc. **S. Forlani:** A. Employment/Salary (full or part-

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Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 763.05/B106

Topic: C.03. Parkinson’s Disease

Title: Modulation of LRRK2 kinase activity by a fragment of its COR domain

Authors: *A. SCHAFFNER[1], X. LI[2], Y. GOMEZ[3], I. UBARRETXENA[3], Z. YUE[2]; [2]Dept. of Neurol., [3]Dept. of Structural Biol., [1]Icahn Sch. of Med. At Mt. Sinai, New York, NY

Abstract: Mutations in the Leucine-Rich Repeat Kinase (LRRK2) gene have been linked to an autosomal-dominant form of Parkinson’s disease (PD). Early studies in primary neurons show that the toxic effects caused by pathogenic LRRK2 mutations are dependent on a functioning kinase domain. Therefore, a number of LRRK2 kinase inhibitors have been reported for therapeutic purposes, though none have succeeded in entering the phase of clinical trials. Beyond its kinase domain, LRRK2 is an active GTPase, contains multiple protein-interacting domains, and is known to form dimers in solution. However, there is little information on the full-length structure of LRRK2 and how its various functions are related. This complexity has motivated us to explore alternative mechanisms for therapeutic intervention. Here we report the study of the COR domain, which is the sequential link between the kinase and GTPase domains and may provide cis regulation of the two enzymatic activities. While previous work showed that the ROC-COR tandem domain could reduce LRRK2 kinase activity *in vitro*, we find that the COR domain alone can modulate LRRK2 kinase activity. We have mapped the inhibitory function to a fragment of COR domain. Furthermore, we find that the fragment of COR forms a dimer in solution. Through biochemical and biophysical analysis, structural modeling and cellular functional assays, we will uncover the precise mechanism by which this modulation of kinase activity occurs. Our study is expected to provide insight into how LRRK2 activity is regulated,

which in turn will assist in the identification of novel therapeutic strategies targeting LRRK2-associated PD.

Disclosures: **A. Schaffner:** None. **X. Li:** None. **Y. Gomez:** None. **I. Ubarretxena:** None. **Z. Yue:** None.

Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

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Topic: C.03. Parkinson’s Disease

Support: R01 NS064934

Michael J. Fox Foundation for Parkinson’s Disease Research

American Parkinson’s Disease Association

Title: LRRK2 mediation of alpha-synuclein aggregation

Authors: ***Y. VOSKOBIYNYK**, L. A. VOLPICELLI-DALEY, A. B. WEST;
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Abstract: Lewy bodies and Lewy neurite inclusions principally comprised of alpha-synuclein are the primary characteristic of late onset Parkinson disease (PD) pathology. Mutations in leucine-rich kinase 2 (LRRK2) are the most common known genetic cause of dominantly inherited PD. Previous studies in model systems have demonstrated a link between LRRK2 and alpha-synuclein in neurodegenerative pathways, although the mechanisms underlying this link are not yet clear. Our goals are to first determine if LRRK2 activity enhances the formation of alpha-synuclein inclusions, and then determine if potential therapeutics that target LRRK2 inhibit alpha-synuclein inclusion formation. We focus efforts in primary neurons cultured from LRRK2 transgenic and knockout rodents that develop Lewy pathology induced by the administration of synthetic alpha-synuclein pre-formed fibrils (PFFs). To attribute changes in susceptibility to alpha-synuclein pathology directly to LRRK2, we further utilize highly potent and selective LRRK2 inhibitors to block LRRK2 kinase activity as well as antisense oligonucleotides to acutely block LRRK2 expression. Our findings are expected to contribute to understanding the efficacy of LRRK2 targeting as a therapeutic approach to ameliorate PD pathophysiology.

Disclosures: **Y. Voskobiynyk:** None. **L.A. Volpicelli-Daley:** None. **A.B. West:** None.

Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

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Topic: C.03. Parkinson's Disease

Support: NIH U18NS082132

NIH T32GM008111

Title: Elevated Ser(p)-1292 LRRK2 in exosomes from Parkinson's disease subjects

Authors: ***K. B. FRASER**[1], R. ALCALAY[2], M. MOEHLE[1], D. STANDAERT[1], A. WEST[1]; [1]Neurol., Univ. of Alabama At Birmingham, Birmingham, AL; [2]Columbia Univ., New York, NY

Abstract: Leucine-rich repeat kinase 2 (LRRK2) mutations are the most common autosomal-dominant cause of Parkinson disease (PD). The penetrance of the most prevalent pathogenic LRRK2 mutation, G2019S, is incomplete, and the effects of the G2019S mutation on LRRK2 kinase activity have not been demonstrated in clinical samples. We evaluated a novel biomarker for LRRK2 kinase activity, Ser(P)-1292 LRRK2, in cell lines and human subjects with and without the G2019S LRRK2 mutation. Ser(P)-1292 LRRK2 was enriched in the kinase-active dimer isoform of LRRK2 protein, and all pathogenic LRRK2 mutations tested increased Ser(P)-1292 LRRK2 levels in transfected cell lines. In human urinary exosomes, G2019S carriers with PD had increased Ser(P)-1292 LRRK2 while asymptomatic G2019S carriers had lower levels. Increased Ser(P)-1292 LRRK2 levels in G2019S LRRK2 carriers with PD support a kinase-activation hypothesis for the mutation. We further evaluated the Ser(P)-1292 LRRK2 marker in urinary exosomes as a biomarker in idiopathic PD cases in a cross-sectional study at the University of Alabama at Birmingham Movement Disorder Program and found there to be a significant increase in Ser(P)-1292 LRRK2 in idiopathic PD cases versus healthy age and gender matched controls. We also observed a correlation between this marker and PD severity. Further studies are required in longitudinal cohorts to evaluate the potential of Ser(P)-1292 LRRK2 levels in the diagnosis and prognosis of PD.

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Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

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Topic: C.03. Parkinson's Disease

Support: MJFF LRRK2 in Idiopathic PD program

NIH/NIGMS Training in Integrative and Systems Biology: Neuroscience T32 GM08605-10 (PI: Smith, Y)

NIH Immunology T32 Training Grant recipient 5T32AI007610-14 (PI: Evavold, B)

Title: The role of LRRK2 in inflammaging and Parkinson's disease

Authors: *E. M. KLINE, D. A. COOK, G. T. KANNARKAT, J. CHANG, J.-K. LEE, J. M. BOSS, M. G. TANSEY;
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Abstract: As individuals age, they become more susceptible to infections and the development of serious life-threatening diseases such as cancer, Alzheimer's and Parkinson's disease (PD). The immune system functions to prevent and fight infection as well as repair damaged tissues. Over time, a phenomenon known as immunosenescence occurs, where immune function becomes dysregulated leading to both a persistent low level inflammation and an increased susceptibility to development of disease. Leucine rich repeat kinase 2 (LRRK2) is a protein highly expressed in immune cells that has been reported as a negative regulator of nuclear factor of activated T cells (NFAT), a transcription factor essential to proper T cell function and activation. The *lrrk2* locus is associated with many immunological diseases, including Parkinson's disease, Crohn's disease, and increased risk for *Mycobacterium leprae* infection, indicating that it plays an important role in proper immune function. As reported in the literature, we have confirmed that LRRK2 is expressed in cells of the immune system (CD4+ and CD8+ T cells, CD14+ monocytes, and CD19+ B cells). In addition, we have established that there are time dependent changes in LRRK2 within T cells subsets upon activation. The relative expression levels in individual subsets of immune cells are not currently known. It is also not known how LRRK2 expression changes with age. We have found that at baseline, there is greater LRRK2 expression in T cells of subjects with PD. Following stimulation, LRRK2 expression levels increase in both monocytes and T cells, with no differences between PD patients and age-matched, healthy control subjects. We have also found that during T cell proliferation, subjects with PD have greater upregulation of LRRK2 compared to healthy

controls. By determining the role LRRK2 plays in modulating immune function, we will reveal opportunities to develop new therapies to treat or slow progression of age-related diseases involving immune cell dysfunction.

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Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 763.09/B110

Topic: C.03. Parkinson's Disease

Support: Pfizer neuroscience and pain research unit

Title: LRRK2 small molecule inhibitors block α-synuclein-mediated dopaminergic neurodegeneration

Authors: *H. ABDELMOTILIB[1], J. P. DAHER[2], X. HU[1], P. GALATSIS[3], W. D. HIRST[3], A. B. WEST[1];
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Abstract: Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene can cause late-onset Parkinson's disease (PD). These mutations cluster within the catalytic core of LRRK2. Recent work has demonstrated that many of the pathogenic LRRK2 mutations result in an increase in LRRK2 kinase activity. LRRK2 is therefore a potential therapeutic target for small molecule kinase inhibitors. We can demonstrate that inhibition of LRRK2 kinase activity by a potent and selective orally-available LRRK2 kinase inhibitor, PF-06447475, significantly attenuates α-synuclein-induced dopaminergic neurodegeneration in a rAAV2-α-synuclein rat model. We extend these findings through utilization of a second class of LRRK2 small molecule inhibitors structurally distinct from PF-06447475 but with similar or superior potency and drug properties. These inhibitors are being used to delineate dose-responsiveness and timing of delivery with respect to α-synuclein induced neurodegeneration. Results from these studies may be useful for the design of additional pre-clinical studies and ultimately clinical trials for LRRK2-targeting therapeutics.

Disclosures: **H. Abdelmotilib:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Pfizer neuroscience and pain research unit. **J.P. Daher:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Pfizer neuroscience and pain research unit. **X. Hu:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Pfizer neuroscience and pain research unit. **P. Galatsis:** A. Employment/Salary (full or part-time):; Pfizer neuroscience and pain research unit. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pfizer neuroscience and pain research unit. **W.D. Hirst:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Pfizer neuroscience and pain research unit. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pfizer neuroscience and pain research unit. **A.B. West:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Pfizer neuroscience and pain research unit.

Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 763.10/B111

Topic: C.03. Parkinson’s Disease

Support: NIH/NINDS F31NS081963

NIH/NINDS R01NS064934

Title: LRRK2 mediates myeloid cell chemotactic responses

Authors: ***M. S. MOEHLE**[1], J. P. L. DAHER[1], T. D. HULL[2], R. BODDU[3], H. A. ABDELMOTILIB[1], J. A. MOBLEY[2], G. T. KANNARKAT[4], M. G. TANSEY[4], A. B. WEST[1];

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Abstract: The *Leucine rich repeat kinase 2* (*LRRK2*) gene is genetically and biochemically linked to several diseases that involve innate immunity. LRRK2 protein is highly expressed in cells of the immune system, most notably in myeloid cells capable of mounting potent pro-inflammatory responses. We and others have shown that knockdown of LRRK2 protein results in reduced pro-inflammatory responses and fewer myeloid cells recruited to the brain after insult. To study the effect of LRRK2 pathogenic mutations that cause Parkinson's disease on myeloid cell function, we utilized rats expressing G2019S LRRK2 from a human bacterial-artificial chromosome. G2019S-LRRK2 expression caused an exaggerated pro-inflammatory response and subsequent neurodegeneration after lipopolysaccharide injections in the substantia nigra, with a marked increase in recruitment of CD68 myeloid cells to the site of injection. While G2019S LRRK2 expression did not affect cytokine or chemokine release or phagocytosis, myeloid cells expressing G2019S LRRK2 showed enhanced chemotaxis both *in vitro* in two-chamber assays as well as *in vivo* in response to thioglycollate injections in the peritoneum. The G2019S mutation enhanced the association between LRRK2 and actin-regulatory proteins that control chemotaxis, and this interaction and the enhanced chemotaxis can be blocked by LRRK2 kinase inhibitors. In order to better understand how LRRK2 kinase activity may modulate actin-regulatory networks important for chemotaxis, we employed an unbiased SILAC based whole-phosphoproteomic approach in primary macrophage cells. Differential phosphorylation of actin-regulatory protein complexes may explain the effect of LRRK2 kinase inhibitors on myeloid cell chemotaxis. Taken together, these results suggest that the primary mechanism of G2019S LRRK2 with respect to myeloid cell function in disease may be related to exaggerated chemotactic responses through up-regulation of actin-mediated cell motility.

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Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

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Topic: C.03. Parkinson's Disease

Support: NIH/NINDS R01NS064934

NCI P30CA013148

Title: Lrrk2 autophosphorylation enhances gtpase activity

Authors: *Z. LIU[1], L. DELUCAS[2], W. ANDREW[3];
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Abstract: The leucine rich repeat kinase 2 (LRRK2) protein possesses both GTPase and kinase activities, with mutations in either enzymatic domain resulting in late-onset Parkinson disease (PD). GTPase proteins are critical upstream modulators of many protein kinases, but in LRRK2, the kinase domain autophosphorylates several amino acids within its own GTPase domain (known as ROC) which might regulate the GTPase activity. Pathogenic mutations up-regulate autophosphorylation of the ROC domain. Despite predictions using the crystal structure of ROC that suggests phosphorylation of the nucleotide pocket would block nucleotide binding, we find that autophosphorylated ROC has normal nucleotide binding properties. Despite normal off-rates of nucleotide, the GTPase activity of autophosphorylated ROC is stimulated compared to non-phosphorylated ROC. ROC dimerization has been implicated in GTPase activity, and we found that autophosphorylation of ROC promotes the formation of GDP-bound protein dimers. However, we found equivalent GTPase activity associated with monomeric and ROC dimers, suggesting the increased GTPase activity in autophosphrylated ROC is not due to ROC dimerization. Molecular modeling predictions based on the local effects of phosphorylation show that the addition of phosphates, particularly to the p-loop residues, may enhance GTP hydrolysis through promoting the catalytic action of bound magnesium. Mining the phospho-proteome database revealed that phosphorylation in equivalent p-loops occurs in many other well-known GTPases including members of the Rab and Rho superfamilies. Therefore phosphorylation might be a common mechanism in regulation of GTPase activity. The unique configuration and biochemistry of LRRK2 has uncovered a novel mechanism for kinase-mediated control of GTPase activity that warrants further exploration in both LRRK2 and other GTPases.

Disclosures: **Z. Liu:** None. **L. DeLucas:** None. **W. Andrew:** None.

Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 763.12/C1

Topic: C.03. Parkinson’s Disease

Title: Identification and Characterization of a novel LRRK2 kinase inhibitor: ODS2005294

Authors: *B. SPINNEWYN[1], C. BERTHET[2], G. MAUTINO[1], O. LAVERGNE[1], P. BLOM[2], J. HOFLACK[2];
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Abstract: Leucine-rich repeat kinase 2 (LRRK2) has been identified as a potential target for disease-modifying therapy in Parkinson's disease (PD) because mutations in its catalytic core have been associated with both autosomal-dominant and late-onset sporadic PD. Most described LRRK2 mutations and notably the well characterized G2019S, enhance kinase activity suggesting that small molecule LRRK2 kinase inhibitors may serve as potential therapeutic agents Our strategy was to design and develop LRRK2 kinase inhibitors crossing the blood-brain barrier (BBB) using the Nanocyclix® technology based on small macrocycles that readily cross the BBB. One of our lead compounds, ODS2005294 was shown to exert potent inhibition on LRRK2 *in vitro* (IC_{50} = 9 nM and K_i = 0.6 nM), with cellular activity (IC_{50}) of 79 and 52 nM on hWt and hG2019S transfected cells, respectively. Of 386 profiled kinases, only 7 demonstrated more than 50% inhibition at 0.1µM of ODS2005294. *In vivo*, ODS2005294 administered by oral route was cleared rapidly from plasma and demonstrated good brain penetration (total Brain/Plasma ratio = 4.4). In CD1 or BAC transgenic mice expressing human LRRK2 protein (Wt or G2019S mutation) robust concentration-dependent knockdown of pLRRK2 in brain and peripheral tissues (kidney and PBMC) was observed (from 15 to 100 mg/kg), based on p Ser935 levels and measured compound concentrations. Based on its encouraging *in vitro* and *in vivo* profile, ODS was progressed further to early *in vitro* and *in vivo* toxicological studies. This compound provides a starting point for developing a candidate that could ultimately be used to address the therapeutic benefit of inhibiting LRRK2 in Parkinson's patients harboring the LRRK2 G2019S mutation.

Disclosures: B. Spinnewyn: A. Employment/Salary (full or part-time):; IPSEN INNOVATION. **C. Berthet:** A. Employment/Salary (full or part-time):; Oncodesign. **G. Mautino:** A. Employment/Salary (full or part-time):; IPSEN. **O. Lavergne:** A. Employment/Salary (full or part-time):; IPSEN. **P. Blom:** A. Employment/Salary (full or part-time):; Oncodesign. **J. Hoflack:** A. Employment/Salary (full or part-time):; Oncodesign.

Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

Location: Hall A

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Topic: C.03. Parkinson's Disease

Support: Wellcome Trust Grant 095010/B/10/Z

MRC Grant MR/M00676X/1

Title: The protective R1398H LRRK2 variant affects GTPase activity and canonical Wnt signalling

Authors: *D. C. BERWICK[1,2], J. NIXON-ABELL[1,3], S. GRANNO[1], V. A. SPAIN[1], C. BLACKSTONE[3], K. HARVEY[1];
[1]UCL Sch. of Pharm., Univ. Col. London, London, United Kingdom; [2]Life, Hlth. and Chem. Sci., The Open Univ., Milton Keynes, United Kingdom; [3]Natl. Inst. of Neurolog. Disorders and Stroke, NIH, Bethesda, MD

Abstract: Hereditary mutations in *LRRK2* are a common cause of Parkinson's disease (PD), yet how these mutations act, and indeed the basic function of LRRK2 protein, is disputed. A further *LRRK2* single nucleotide polymorphism, encoding an R1398H amino acid substitution within the LRRK2 Roc domain, has been reported and is suggested to confer protection from PD. Despite this tantalising possibility, the LRRK2 R1398H variant remains almost entirely unstudied in cellular and *in vitro* assays. Here, we present evidence that R1398H affects LRRK2 function in the opposite manner to pathogenic mutants. In contrast to PD-causing mutations within the LRRK2 Roc and COR domains, LRRK2 R1398H displays elevated GTPase activity. Remarkably, and in contrast to pathogenic mutations throughout LRRK2, R1398H enhances canonical Wnt signalling. Providing a mechanistic explanation for these observations, we use molecular modelling to show that arginine-1398 lies in close spatial proximity to PD-causing mutations in the Roc and COR domains, and is likely to affect intramolecular Roc-COR domain interactions. Taken together, our data suggest that the protective and pathogenic effects of LRRK2 mutants may be mediated by increased and decreased canonical Wnt activity, respectively; and that R1398H is indeed a *bona fide* protective mutation. In light of the neuroprotective role of Wnt signalling, our data could have important implications for the treatment of PD.

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Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

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Topic: C.03. Parkinson's Disease

Support: MWU Intramural Funds

Title: Nicotine improves abnormal mitochondrial morphology but not turnover in Parkin loss-of-function *Drosophila* dopaminergic neurons that modulate motor behavior

Authors: *L. M. BUHLMAN[1], J. CACKCOVIC[1], G. B. CALL[2], S. GUTIERREZ[1];
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Abstract: Parkinson's disease (PD) is characterized by a selective degeneration of dopaminergic neurons in the substantia nigra *pars compacta*. Mitochondrial pathology is heavily implicated in both sporadic and familial forms of PD, including Autosomal Recessive Juvenile Parkinsonism (ARJP), which is often caused by mutations in the *PARK2* gene. Parkin, the cytosolic ubiquitin ligase product of *PARK2*, has been shown to promote the turnover of mitochondrial import proteins and respiratory chain enzymes. Homozygous $park^{25}$ mutant *Drosophila* have decreased mitochondrial function that selectively affects dopaminergic (DA) neurons. Decreases in mitochondrial function initiate network fragmentation and mitophagy, a quality control mechanism in which mitochondrial networks become fragmented, and poorly functioning organelles are digested by lysosomes. Using 3D image processing in heterozygous Parkin loss-of-function *Drosophila melanogaster* that express a mitochondrially-targeted GFP in Tyrosine hydroxylase-producing cells, we have shown that mitochondria are fragmented and lost in dopaminergic neuronal clusters that are functionally homologous to the mammalian substantia nigra *pars compacta*. In order to explore whether the mechanism by which nicotine administration selectively improves heterozygous Parkin loss-of-function phenotypes in *Drosophila*, we measured mitochondrial network morphology and volume in mutant flies raised on nicotine food and found that nicotine affects mitochondrial morphology, but does not prevent loss of mitochondrial network. Interestingly, mitochondrial network volume was decreased in control flies raised on nicotine food; this result provides insight to the potential mechanism by which nicotine reduces lifespan, climbing and flight capabilities in control flies. Our results shed light on the mechanisms of Parkin loss-of-function pathology, propose that nicotine may improve the mutant phenotype via effects on mitochondrial function, and further substantiate the use of *Drosophila* as a model of ARJP.

Disclosures: L.M. Buhlman: None. **J. Cackcovic:** None. **G.B. Call:** None. **S. Gutierrez:** None.

Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

Location: Hall A

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Program#/Poster#: 763.15/C4

Topic: C.03. Parkinson's Disease

Support: NIEHS grant ES010975

Columbia University Provost Fellowship

Title: Lack of dopaminergic neuron degeneration in the substantia nigra pars compacta of non-human primates with chronic manganese exposure

Authors: *K. K. GONZALES[1], J. MCGLOTHAN[1], K. H. STANSFIELD[1], J. S. SCHNEIDER[2], T. R. GUILARTE[1];
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Abstract: Movement abnormalities caused by chronic manganese (Mn) intoxication clinically resemble but are not identical to those in idiopathic Parkinson's disease (iPD), a disorder linked to the progressive, large-scale degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc). Clinical evidence from individuals with Mn-induced parkinsonism has revealed functional dopaminergic terminals in the striatum, along with an unresponsiveness to the anti-parkinsonian dopaminergic drug levodopa (Perl & Olanow, 2007). In agreement, pre-clinical data from our laboratory has shown markedly impaired dopamine release from intact nigrostriatal dopaminergic axon terminals in Mn-exposed monkeys (Guilarte, 2006, 2008). However, in-depth pathological studies as performed in iPD patients and parkinsonian animal models are still needed for Mn-induced parkinsonism. We used a non-human primate model of Mn-induced neurotoxicity to determine if Mn-induced parkinsonism involves degeneration of SNpc dopaminergic neurons. We collected serial sections (1:8) from the entire rostrocaudal extent of the dopaminergic midbrain for unbiased stereological cell counts of tyrosine hydroxylase (TH)-immunoreactive neurons using the optical fractionator principle (Visiopharm). Preceding stereological quantification, we performed a pilot study (n=3 animals; 3 sections per animal; 489 neurons) that revealed optimal antibody penetration throughout the tissue sections (25 μm thickness after processing) and a low coefficient of error (0.023) indicating sufficient precision. Our findings from stereological analyses demonstrate that the total number of TH-positive neurons (N) in the SNpc did not significantly differ between the control (n=4) and Mn-exposed groups (n=5) (t-test; $p = 0.07$), representing the first stereological quantification of TH-positive SNpc cell numbers in Mn neurotoxicity. Follow-up studies will investigate TH-positive neuron numbers in the ventral tegmental area and retrorubral fields, as well as in the precise functional regions of the SNpc. These collective findings suggest that the motor signs of Mn-induced parkinsonism are unrelated to dopaminergic nigral cell loss. Thus, the underlying

pathophysiology of movement disturbances associated with Mn intoxication is different than those present in iPD.

Disclosures: K.K. Gonzales: None. **J. McGlothan:** None. **K.H. Stansfield:** None. **J.S. Schneider:** None. **T.R. Guilarte:** None.

Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

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The Graduate Center, CUNY

Title: Disruption of Parkin integrity by caspase or calpain-cleavage induced by proteasomal or mitochondrial impairment and its prevention by cAMP: relevance to Parkinson's disease

Authors: A. STOLL[1], T. JEAN-LOUIS[3], H. WANG[1], Q. HUANG[1], P. ROCKWELL[1], *M. E. FIGUEIREDO-PEREIRA[2];
[1]Biol. Sci., [2]Hunter Col. CUNY, New York, NY; [3]Biol. Sci., Hunter Col. CUNY, The Grad. Center, CUNY, New York, NY

Abstract: The mechanisms by which Parkin dysfunction contributes to Parkinson disease are poorly delineated. As mitochondrial and proteasomal impairment and inflammation are linked to PD, we investigated the effects of mitochondrial (oligomycin, Oligo) or proteasomal (Epoxomicin, Epox) inhibitors or the product of inflammation prostaglandin J2 (PGJ2), on Parkin integrity in rat midbrain and cortical cultures. Treatments with PGJ2 and Epox induced caspase-cleavage of Parkin while those with Oligo led to calpain-cleavage. Parkin cleavage by caspase was previously shown to be triggered by stress-conditions. However, as far as we know, Parkin cleavage by calpain has not been reported. Upon calpain cleavage, Parkin migrates as a doublet with a slightly larger size than the caspase-mediated fragment. Full length (FL)-Parkin

was localized in the cytosolic, mitochondrial and nuclear fractions. Calpain or caspase-cleaved Parkin were mostly detected in the mitochondrial fraction. We postulate that liberation of the Ubl domain of Parkin by caspase or calpain cleavage facilitates its recruitment to mitochondria. The freed UbL could bind to proteasomes and inhibit their activity. Pre-treatment with the phosphatase inhibitor okadaic acid prior to Oligo treatment, stabilized a higher molecular weight form of FL-Parkin and reduced Parkin cleavage by calpain. This suggests that stabilizing phosphorylation of FL-Parkin with phosphatase inhibitors decreases its susceptibility to calpain-cleavage. Raising intracellular cAMP with PACAP27 (pituitary adenylate cyclase activating peptide) to preserve Parkin integrity prevented its cleavage by caspase but not calpain. Stabilizing intracellular ATP levels with cyclocreatine moderately mitigated Oligo induced calpain cleavage of Parkin. In conclusion, stabilizing FL-Parkin could provide a novel therapeutic strategy for treating PD.

Disclosures: **A. Stoll:** None. **T. Jean-Louis:** None. **H. Wang:** None. **Q. Huang:** None. **P. Rockwell:** None. **M.E. Figueiredo-Pereira:** None.

Poster

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Support: SAF2013-48532 (MINECO)

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CAMref. S2011/BMD-2336

PNSD #2012/071

Title: Role of mutations N370S and L444P of the GBA gene in autophagy and its involvement in Parkinson's disease

Authors: *P. GARCÍA SANZ[1,2], L. ORGAZ GORDILLO[1], I. ESPADAS[1,2], G. BUENO GIL[1], E. RODRÍGUEZ TRAVER[1,2], J. KULISEVSKY[3,2], R. GONZÁLEZ-POLO[4,2], J. FUENTES[4,2], A. GUTIÉRREZ PÉREZ[5,2], C. VICARIO ABEJÓN[1,2], R. MORATALLA VILLALBA[1,2]; [1]Neurobiología Funcional y de Sistemas, Cajal Inst. /CSIC, Madrid, Spain; [2]CIBERNED, Inst. de Salud Carlos III, Madrid, Spain; [3]Movement Disorders Unit, Neurol. Dept., Hosp. de la Santa Creu i Sant Pau, Barcelona, Spain; [4]Dept. de Bioquímica y Biología Mol. y Genética, F.

Enfermería y T.O., Univ. de Extremadura., Cáceres, Spain; [5]Dept. Biología Celular, Genética y Fisiología,, Facultad de Ciencias, Inst. de Investigación Biomédica de Málaga (IBIMA), Univ. de Málaga, Málaga, Spain

Abstract: Parkinson's disease (PD) is one of the most common neurodegenerative disorders. The major motor features of PD are the result of the loss of dopamine neurons in the substantia nigra pars compacta (SNpc) of the midbrain. Despite extensive experimental effort, the cause of neuronal degeneration in PD is not fully understood. Mitochondrial dysfunction, oxidative stress, abnormal protein handling, excitotoxicity, and apoptotic and inflammatory processes have been implicated in the cascade of events leading to loss of dopaminergic neurons in the SNpc. A growing body of evidence show that mutations in the glucocerebrosidase (*GBA*) gene, which encodes the lysosomal enzyme that is deficient in Gaucher's disease (GD), are important and common risk factors for PD. However, the mechanisms by these mutations predispose to cell death remain unclear. Fibroblasts share the genetic complexity of neurons and represent an easily accessible source of proliferating cells, making them a unique patient-specific cellular model of different neurodegenerative diseases. To study the role of heterozygous GBA mutations in the pathology of PD, we generated fibroblast lines from skin biopsies of five PD patients with heterozygous GBA mutation carriers (N370S and L444P) and four controls. We found that both GBA mutations present significantly reduced level of GCase protein and enzyme activity as well as an altered autophagy flux and lysosomal function due to an accumulation of misfolded proteins in endoplasmic reticulum.

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Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

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Topic: C.03. Parkinson's Disease

Support: Yonsei University University-industry Foundation Grant 2014064545

Title: Identification of transglutaminase 2 as a novel substrate of PINK1 and its physiological consequence of Lewy body formation in Parkinson's disease

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Abstract: Parkinson's disease (PD) is the most prominent and progressive movement disorder. PINK1 gene mutations cause one form of autosomal recessive early-onset PD. PINK1 encodes a serine/threonine protein kinase which protects cells from stress-induced mitochondrial dysfunction. Transglutaminase 2 (TG2) is an intracellular protein cross-linking enzyme that has an important role in Lewy body formation during PD pathogenesis. This study identifies PINK1 as a novel TG2 binding partner and shows that PINK1 stabilizes the half-life of TG2 via inhibition of TG2 ubiquitination and subsequent proteasomal degradation. PINK1 affects TG2 stability in a kinase-dependent manner. In addition, PINK1 directly phosphorylates TG2 in carbonyl cyanide m-chlorophenyl hydrazine-induced mitochondrial damaged states, thereby enhancing TG2 accumulation and intracellular protein cross-linking products. This study further confirms the functional link between upstream PINK1 and downstream TG2 in *Drosophila* melanogaster. These data suggest that PINK1 positively regulates TG2 activity, which may be closely associated with aggresome formation in neuronal cells.

Disclosures: B. Min: None. **S. Lee:** None. **H. Rhim:** None. **K.C. Chung:** None.

Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

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Support: JSPS KAKENHI Grant 26870114

Title: An evolutionarily conserved RAB7L1-LRRK2 pathway regulates lysosome integrity and neurite morphology

Authors: *T. KUWAHARA[1,2], K. INOUE[2], T. IWATSUBO[1], A. ABELIOVICH[2];
[1]Univ. Tokyo Grad Sch. Med., Tokyo, Japan; [2]Dept Pathology, Cell Biol. and Neurol., Columbia Univ., New York, NY

Abstract: Mutations in leucine-rich repeat kinase 2 (LRRK2) are the major genetic cause of Parkinson's disease (PD). We previously identified RAB7-like variant 1 (RAB7L1) as an

interactor of LRRK2: RAB7L1 and LRRK2 cooperatively modulates neurite morphology, intracellular trafficking and PD risk. However, the detailed physiological and genetic relationships between LRRK2 and RAB7L1 are still unclear. Here we provide evidence that LRRK2 and RAB7L1 normally serve essential cellular roles in the maintenance of lysosome function and neurite morphology in diverse organisms. Mice deficient in either RAB7L1 or LRRK2 display prominent age-associated lysosomal defects in kidney proximal tubule cells, in the absence of frank CNS pathology. *C. elegans* mutants deficient in orthologues of LRRK2 or RAB7L1 harbor lysosome and axon morphologic abnormalities in neurons. We further identified a retromer and a lysosomal adaptor protein complex that link RAB7L1/LRRK2 dysfunction to lysosomal and neurite abnormalities. These data underscore the evolutionarily conserved role of RAB7L1-LRRK2 pathway in diverse cellular contexts.

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Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

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Hellenic General Secretariat of Research and Technology; 09SYN-12-876

Title: Differential kinase function between dimeric/oligomeric and monomeric LRRK2 species isolated from size exclusion chromatography fractions

Authors: M. LEANDROU[1], K. MELACHROINOU[1], A. MEMOU[1], L. STEFANIS[1,2], *H. J. RIDEOUT[1];
[1]Biomed. Res. Foundation, Acad. of Athens, Athens, Greece; [2]2nd Dept. of Neurol., Univ. of Athens Med. Sch., Athens, Greece

Abstract: The ROCO/RIP kinase protein LRRK2, mutations in which are causally linked to Parkinson’s disease (PD), exists in a broad range of monomeric to highly oligomeric species regulated by a multitude of factors. Multiple groups have reported that mutations associated with PD can enhance the formation of cytoplasmic skein-like filaments, which have been suggested to be highly oligomeric. This phenomenon is linked to the phosphorylation status of a cluster of Ser

residues located in the N-terminal region of the protein; and subsequently, the binding of 14-3-3 to LRRK2. The significance of this redistribution of LRRK2 to highly oligomeric species is not fully understood; nor is the impact of oligomerization on the function or activity of LRRK2. Multiple lines of evidence suggest that the dimeric conformation of LRRK2 possesses greater kinase activity, however it is not clear whether this distinction is unique to membrane-localized LRRK2, or in other compartments as well. Wild type LRRK2 displays a broad range of elution between low and high molecular weight fractions by size exclusion chromatography (SEC). We detect a significant shift in elution towards higher molecular weight fractions in most of the pathogenic PD mutations in LRRK2. Mutations localized within the kinase domain enhance phosphorylation of a peptide substrate in discrete fractions, as opposed to a global increase in activity across all fractions where LRRK2 is detected. However, SEC alone cannot discriminate between truly dimeric or oligomeric species of LRRK2 and monomeric LRRK2 that is bound to a large protein complex. We have developed a technique to selectively label and purify functionally active dimeric/oligomeric LRRK2 species from mammalian cells. With this approach we can not only quantify dimeric or oligomeric LRRK2 eluted from SEC-derived fractions; but also we can also directly compare multiple features of LRRK2 kinase activity within each sub-pool of LRRK2 species. This platform can also be exploited to screen for LRRK2 kinase inhibitors with a selective affinity for certain LRRK2 conformations or species.

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Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

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Topic: C.03. Parkinson’s Disease

Support: NIH Grant NS060872-05

Title: Post-transcriptional regulation of α-synuclein by lrrk2 through interactions with micrornas in Parkinson’s disease

Authors: *J. BOON;
Pharmacol., Boston Univ. Sch. of Med., Boston, MA

Abstract: Recent studies have suggested that specific RNA transcript isoforms of α-synuclein with an extended 3’ untranslated region (UTR) are selectively linked to Parkinson’s pathology,

relative to α-synuclein with short 3'UTR. 3'UTR is a target region for RNA binding proteins and microRNAs, which lead to regulation of translation. LRRK2 is the most commonly mutated gene in Parkinson's Disease and studies have shown that it has a role in translation. In this study, we hypothesize that the expression and toxicity of α-synuclein are regulated by LRRK2 post-transcriptionally through interactions with microRNAs. Our data shows that LRRK2 modulates α-synuclein translation. In HEK293FT cells, co-expression of α-synuclein with either long or short 3' UTR and wild-type LRRK2 lead to a significant increase in α-synuclein expression relative to without LRRK2 as measured by florescence level of the GFP-tagged α-synuclein and there is a greater increase in the condition with short relative to long 3'UTR. In primary culture neurons, α-synuclein transcript isoform with short 3'UTR has higher expression level relative to isoform with long 3'UTR in the presence of LRRK2 as well. In addition, in conditions of α-synuclein with short 3'UTR together with LRRK2, neurons demonstrate a broader distribution of α-synuclein, along with a greater number of α-synuclein containing puncta along the processes. This data suggests a differential effect of LRRK2 on α-synuclein with either short or long 3'UTR's expression and distribution. Also, by co-staining with Mitotracker dye, our data shows co-localization of α-synuclein with mitochondria along the processes of primary culture neurons. Next, we investigated whether regulation of α-synuclein expression by LRRK2 require the binding of microRNAs. The short 3'UTR sequence of α-synuclein has a binding site for miR-7 and the long 3'UTR has binding sites for both miR-7 and miR-153. We performed site-directed mutagenesis where we mutated the binding site for miR-7 on the short 3'UTR and that for miR-7 or miR-153 on the long 3'UTR, so these microRNAs can no longer bind. Deletion of the miR-7 site abolished all effects of LRRK2 on expression of α-synuclein with short or long 3'UTR. In contrast, deleting the miR-153 site resulted in a moderate decrement in the expression of the long 3'UTR α-synuclein. We further investigate whether the kinase domain of LRRK2 is involved in the observed differences. We employed LRRK2-specific kinase inhibitor, LRRK2-IN-1, and our data shows that inhibition of the kinase domain of LRRK2 decreases the level of α-synuclein protein expression. For future studies, we will measure direct effects of LRRK2 on microRNAs productions.

Disclosures: J. Boon: None.

Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

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Topic: C.03. Parkinson's Disease

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CAPES (Brazil)

Title: The kinin system in the 6-hydroxy-dopamine model of Parkinson´s disease

Authors: *L. M. DATI, L. R. G. BRITTO;
Univ. of Sao Paulo, Sao Paulo, Brazil

Abstract: Parkinson´s disease (PD) involves loss of dopaminergic neurons of the substantia nigra, which produces marked motor and cognitive disorders. PD has been studied with several approaches, including animal models such as the 6-OH-dopamine intrastriatal injection. There is evidence on the possible participation of neurotransmitters and receptors in the development of neurodegeneration and neuroprotection processes. For example, kinins, through their actions on B1 and/or B2 receptors, may be involved with neuroprotection. In this study, we sought to investigate a possible participation of the kinins in the pathophysiology of PD-like condition in the mouse, by means of immunohistochemistry, Western blotting, pharmacological approaches and the use of a B2 knockout mouse. Tyrosine-hydroxylase immunolabeling in wild-type mice (C57BL/6) was reduced by about 50% both in the striatum and the substantia nigra on the side ipsilateral to the 6-OH-dopamine injection in relation to the contralateral side, injected with saline. After toxin injections in the B2 knockout mouse, we observed a much smaller reduction of tyrosine-hydroxylase protein expression (ca. 10%; $p<0.001$). A very similar effect was observed with the use of intrastriatal HOE-140 (100 nM), a specific antagonist of the B2 receptor. Intrastriatal administration of bradykinin (10 μM) also produced a smaller reduction of tyrosine hydroxylase in the striatum (ca. 30%; $p<0.05$) but a slightly higher drop in the substantia nigra (ca. 60%; $p<0.05$) in relation to untreated PD-like animals. Immunolabeling for an astrocyte marker, glial fibrillary acidic protein (GFAP), was reduced in the striatum of B2 knockout mouse injected with the toxin in relation to wild-type injected mice (ca. 30%; $p<0.05$). Bradykinin-treated PD mice exhibited very small GFAP increases (ca. 15%; $p<0.05$ vs untreated mice), but HOE-140 produced unconsistent data in regard to astrocytic activation. These results indicate a possible participation of the kinin system in the pathophysiology of PD, which remains to be further characterized.

Disclosures: L.M. Dati: None. **L.R.G. Britto:** None.

Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

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Title: Characterizing the role of prolyl oligopeptidase in mouse nigrostriatal dopaminergic and GABAergic systems

Authors: *U. JULKU, R. SVARCBAHS, M. SAVOLAINEN, S. TIILIKAINEN, T. MYÖHÄNEN;
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Abstract: Aplha-synuclein (aSyn) is the main component of the Lewy bodies, a histopathological finding of Parkinson's disease (PD). Prolyl oligopeptidase (PREP) is a serine protease that accelerates aggregation of aSyn *in vitro*, and PREP enzyme inhibitors have shown to block the aggregation process *in vitro* and in cellular models, and also enhance the clearance of aSyn aggregates in transgenic mice models. In addition, PREP is shown to be colocalized with aSyn in the post mortem PD brain. However, although PREP has several known substrates, the physiological and pathological roles have remained unclear. PREP inhibitors have caused some alterations in dopamine (DA) and metabolite levels in the striatum and substantia nigra, and PREP localizes GABAergic neurons of nigrostriatal tract and in some extent in DAergic neurons, but the functions of PREP in nigrostriatal pathway are unclear. Moreover, aSyn is shown to have physiological functions in DA release and storage in nigrostriatal pahtway. The aim of the study was to to characterize the role of PREP in nigrostriatal DAergic and in GABAergic systems of C57Bl/6 and PREP knock-out mouse, and the effects of PREP overexpression by AAV-hPREP or PREP inhibition (small molecule inhibitor KYP-2047) on these systems by using microdialysis and HPLC analysis. Single injection or 5-day treatment by KYP-2047 did not have effect on concentration of DA, its metabolites, glutamate or GABA in tissues of striatum and substantia nigra or extracellular concentration of DA and GABA in striatum measured by microdialysis in young C57Bl/6 mice. Overexpression of PREP in nigrostriatal tract by nigral AAV-hPREP injection did not have effect on extracellular concentrations of DA and DOPAC in striatum but increased HVA and 5-HIAA at 5 weeks as measured by microdialysis. There was also statistically significant difference in d-amphetaminesulphate induced DA release. AAV-hPREP seems to decrease locomotor activity slightly at 4 weeks post-injection but the difference is not statistically signigficant. Lack of PREP did not have effect on baseline level of striatal extracellular DA or its metabolites in microdialysis study in PREP knock-out mice but d-

amphetaminesulphate induced DA release was lowered when PREP expression was restored by nigral AAV-hPREP injection. Results suggest that PREP and PREP inhibitor do not affect basal DA and GABA release directly but overexpression of PREP causes alterations on induced dopamine release and baseline levels of HVA and 5-HIAA. This suggests that of PREP could contribute to release of neurotransmitters in nigrostriatal pathway but the mechanisms needs to be studied further.

Disclosures: U. Julku: None. **R. Svarcbahs:** None. **M. Savolainen:** None. **S. Tiilikainen:** None. **T. Myöhänen:** None.

Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

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Topic: C.03. Parkinson's Disease

Support: FP7 CIG 303797

Wellcome Trust WT097829MF

Title: Classification of Parkinson's disease genotypes in *Drosophila* using spatiotemporal profiling of vision

Authors: *A. R. WADE[1], R. J. H. WEST[2], C. J. H. ELLIOTT[2];
[1]Univ. of York, Heslington, United Kingdom; [2]Biol., Univ. of York, York, United Kingdom

Abstract: Electrophysiological studies have demonstrated altered contrast processing in Parkinson's Disease (PD) patients. Here we asked whether multivariate data extracted from steady-state visually-evoked potentials (SSVEPs) in *Drosophila* could be used to identify different PD mutations. Flies from four control lines were compared to three early-onset PD mutations (PINK1, DJ-1α and DJ-1β) and one mutation in the fly LRRK2 orthologue (dLRRK). Results from supervised machine learning indicate that this is a promising technique for rapid phenotyping of PD-related mutations in an animal model. Methods: Stimuli were dynamic, contrast reversing grating stimuli, spanning 64 spatiotemporal frequency combinations (8 spatial x 8 temporal frequencies). We recorded the second harmonic of the SSVEP generated by the contrast reversal across all combinations using a single-channel ERG electrode. A supervised linear classifier combined with an iterative dimensionality reduction algorithm was used to estimate classification accuracy for a) Each pair of genotypes, b) PD vs Control genotypes and c)

Each individual genotype within the entire set. Statistical significance was computed using a bootstrap procedure and a leave-one-out procedure. Data from 180 flies are presented. Results The patterns of neuronal responses differed between genotypes. Wild-type and early-onset PD flies formed separate clusters in the high-dimensional data space and the late-onset mutation was an outlier. This clustering was preserved in a multidimensional scaling analysis. Neuronal responses in early-onset PD flies were, in general, stronger than in wild-types and multivariate pattern analysis assigned flies to PD or non-PD genotypes with an accuracy >85%. Conclusion There are reliable and significant differences in the evoked visual responses of flies carrying different PD-related mutations. These differences can be used to assign flies to the correct genotype with high accuracy. As well as aiding in the use of *Drosophila* to study the mechanisms of PD and in drug discovery, we propose that machine learning algorithms may also be useful in increasing the diagnostic specificity of human electrophysiological measurements.

Disclosures: A.R. Wade: None. **R.J.H. West:** None. **C.J.H. Elliott:** None.

Poster

763. LRRK2 and Other Mechanisms in Parkinson's Disease

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Title: Levodopa-induced motor behavior alterations in *Drosophila* larvae

Authors: A. DERGAN, J. STANTON, R. GOUGH, B. DIEDERICH, *B. A. CHASE;
Dept Biol, Univ. Nebraska-Omaha, Omaha, NE

Abstract: Dyskinesias associated with dopamine-replacement therapy pose therapeutic challenges for individuals with Parkinson’s Disease. A better understanding of their physiological basis holds promise for more effective management of these anomalous motor behaviors. Not all patients receiving dopamine-replacement therapy develop dyskinesias, suggesting the hypothesis that the degree of dyskinesia development is a quantitative trait that can be influenced by genetic variants. Since motor behavior in a wide range of animals is influenced by dopaminergic function, observations from model organisms can provide meaningful insights with human application. Therefore, we are taking an unbiased approach to identify *Drosophila* quantitative trait loci (QTL) that influence the motor responses to levodopa treatment. We present data showing the viability of this approach. Motor behavior was assayed

in third-instar larvae fed L-dopa in 3% sucrose for 15 minutes. Quantitative analysis of locomotory behavior following levodopa treatment identifies motor behaviors that are differentially responsive to levodopa. Larvae fed 0.58 mM L-dopa in 3% sucrose, compared to controls fed only sucrose, show increases in contractions per minute ($t(84) = -8.499$, $p < .001$) and turns per minute ($t(81) = -9.952$, $p < .001$), and a modest decrease in bends per minute ($t(82) = 2.039$, $p = .045$). L-dopa also induces two novel uncoordinated behaviors: “stagger”, an anterior lateral tilt immediately before or during a contractile motion, and a “horizontal tail flip”, a posterior lateral bend during a contractile motion. Since wild strains of *Drosophila* show substantial genetic variation, we are currently evaluating variation in these responses among such strains as a prelude to identifying responsible QTLs.

Disclosures: A. Dergan: None. **J. Stanton:** None. **R. Gough:** None. **B. Diederich:** None. **B.A. Chase:** None.

Poster

764. Neuroprotective Mechanisms in Parkinson's Disease

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 764.01/C15

Topic: C.03. Parkinson’s Disease

Support: NIH R01 NS065338-01 A2

Title: Potential role of FosB and ΔFosB in the differential long-term regulation of parkin expression in central dopaminergic neurons in response to acute neurotoxicant exposure

Authors: *J. PATTERSON[1], K. LOOKINGLAND[2], J. L. GOUDREAU[3];
[2]Pharmacol. and Toxicology, [3]Dept. of Neurol., [1]Michigan State Univ., East Lansing, MI

Abstract: A characteristic of Parkinson disease (PD) is the progressive loss of nigrostriatal dopamine (NSDA) neurons. In mice, these neurons can be preferentially damaged through exposure to the neurotoxicant 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Another population of DA neurons that respond to MPTP, but are able to recover is the tuberoinfundibular DA (TIDA) neurons whose recovery is correlated with an increase in parkin mRNA and protein. Parkin is a product of the PARK2 gene, which is linked to autosomal recessive or juvenile PD. Parkin has multiple functions in neurons and is predicted to protect against the neurotoxic effects of MPTP. Differential expression of transcription factors that regulate the parkin promoter could explain the differential susceptibility of DA neurons. The parkin promoter is bi-directional consisting of an approximately 200 bp segment of DNA that

regulates the expression of the PARK2 gene as well as parkin co-regulated gene. Potential transcription factors of parkin were identified using TFSEARCH and PROMO. One predicted transcription factor of parkin is Activator Protein 1 (AP-1), which is a heterodimer composed of proteins from the Fos, Jun, and ATF families. In the present study the temporal expression of FosB and ΔFosB were measured after acute neurotoxicant administration. Male C57BL/6j were injected with 20 mg/kg MPTP (sc) and decapitated at 4, 6, 8, 12, or 24 h post-injection. Control mice were injected with saline (10 mL/kg; sc) and killed 24 later. Brains were frozen, sectioned, regions containing the cell bodies of the TIDA (arcuate nucleus; ARC) and NSDA (substantia nigra; SN) neurons were dissected and processed for Western blot analysis. The results reveal that expression of FosB and ΔFosB correlates with parkin, increasing in the ARC and not in the SN. As ΔFosB is a highly stable truncated form of FosB, both FosB/ΔFosB and parkin were measured 1, 3, and 7 days after a single injection of 20 mg/kg MPTP (sc). Elevated ΔFosB and parkin protein levels were observed over all seven days in the ARC, but did not change in the SN. These results reveal that expression of FosB and ΔFosB correlate with the differential expression of parkin, increase prior to parkin, and are predicted to bind the parkin promoter sequence, which suggests that FosB and ΔFosB may act to regulate parkin expression in response to neurotoxicant exposure.

Disclosures: J. Patterson: None. **K. Lookingland:** None. **J.L. Goudreau:** None.

Poster

764. Neuroprotective Mechanisms in Parkinson's Disease

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Support: 973 program of China (2011CB510004)

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SHIAE grant BME46/14

Title: Identification of neuro-protective genes during the progression of dopaminergic cell loss in zebrafish

Authors: *S. L. WALKER[1], S.-C. CHEN[2], W.-H. YUNG[3], Y. KE[3];
[2]Sung Hing Inst. of Advanced Engin., [3]Sch. of Biomed. Sci., [1]The Chinese Univ. of Hong Kong, Shatin, Hong Kong, Hong Kong

Abstract: The neurodegenerative disorder Parkinson's disease (PD) is among the most debilitating diseases currently afflicting the aging population. Extensive studies into the onset and progression of Parkinson's disease have elucidated multiple genes affected during dopaminergic cell loss. However, the extent of networks involved in the progression of PD is still largely undefined. This limits testing of potential therapeutic gene targets to a handful of gene candidates. As a means to identify potential gene networks involved in neural protection, we utilized temporal microarray data during various neuronal ablation paradigms from the zebrafish model. Here we identified multiple genes potentially involved in neural protection, some of which are currently being targeted in the literature as important neuro-protective factors, during dopaminergic neuronal cell death. In this study we tested the potential role of Glutathione Reductase (GSR), Major Vault Protein (MVP), ZGC:174888, and other candidates during dopaminergic neuronal cell death in the zebrafish model. Following treatment with 6-OHDA, a chemical which induces dopaminergic neuronal cell death, the extents of dopaminergic cell loss and delay in motility were assessed. Gene expression was either silenced using morpholinos and/or chemical inhibitors or overexpressed using chemical activators to define their roles in neuronal cell death and cell survival. *In vivo* time-lapse imaging in conjunction with behavioral studies were utilized to establish the extent of neural cell death and protection of normal behavioral patterns during dopaminergic cell loss.

Disclosures: **S.L. Walker:** None. **S. Chen:** None. **W. Yung:** None. **Y. Ke:** None.

Poster

764. Neuroprotective Mechanisms in Parkinson's Disease

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Topic: C.03. Parkinson's Disease

Support: UNAM PAPIIT IA202214-2

FESI-DIP-PAPCA-2014-18

UNAM PAPIIT IN2151114

FESI-DIP-PAPCA-2014-16

Title: Neurogenesis in hippocampus induced by administration of L-dopa/melatonin in the hemi-Parkinsonian rat

Authors: A. SANCHEZ-SORIA[1], M. MORENO[2], A. GUTIERREZ-VALDEZ[2], M. AVILA-COSTA[2], J. RAMOS-JIMENEZ[3], *V. ANAYA-MARTINEZ[2];
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Abstract: Parkinson disease (PD) is a neurodegenerative disorder of unknown etiology characterized by the loss of dopaminergic neurons in the substantia nigra compacta (SNc), conventional therapy with L-Dopa produces adverse effects after the prolonged period of administration probably due to the generation of free radicals. Melatonin has endogenous antioxidant actions. Previously we concluded that the co-administration of some antioxidants like melatonin with L-Dopa, helps to reverse some alterations induced by L-Dopa treatment and could promote the generation of new dopaminergic neurons in the SNc probably by reducing the oxidative environment. The hippocampus, a nucleus involved in memory processes, have a neurogenic area the dentate gyrus; this nucleus receive dopaminergic innervation from SNc neurons, and the neurogenic capacity is reduced in tissue of people who had PD. This study examines the ability of melatonin (10 mg/kg)/ L-DOPA (7.5 mg/kg) to increase neurogenesis in the hippocampus of the rats with Parkinson's disease model compared to a group with L-DOPA (7.5 mg/kg), a group with melatonin and a control group (sham lesion). During the month of drug treatment they received the injections of neurogenic marker, the BrdU. The neurogenesis in the hippocampus was judged by the counting of neurons with the colocalization of the markers antiBrdU and antiNeuN (neuronal marker). Our data show that the injection of 6-OHDA reduces the presence of BrdU/TH positive, and that the administration of L-dopa and/or melatonin reverses this effect. These results indicate that melatonin can modulate the survival of new neurons in the adult hippocampus.

Disclosures: A. Sanchez-Soria: None. **M. Moreno:** None. **A. Gutierrez-Valdez:** None. **M. Avila-Costa:** None. **J. Ramos-Jimenez:** None. **V. Anaya-Martinez:** None.

Poster

764. Neuroprotective Mechanisms in Parkinson's Disease

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Topic: C.03. Parkinson’s Disease

Support: IZKF N5-1

RWTH Univ. Reentry programme

Title: Rab7 induces clearance of alpha-synuclein aggregates

Authors: *B. H. FALKENBURGER, E. DINTER, T. SARIDAKI, M. NIPPOLD, L. FENSKY, L. DIEDERICHS, A. VOIGT, J. SCHULZ;
RWTH Univ. Aachen, Aachen, Germany

Abstract: Parkinson's disease is characterized and likely caused by aggregates of the protein alpha-synuclein. Using GFP-labelled alpha-synuclein we have previously shown that cells can in principle remove these aggregates. Here we describe the effects of the small GTPase Rab7, which is primarily known for regulating trafficking of late endosomes. We found that Rab7 decorates vesicles containing alpha-synuclein aggregates, and that Rab7 overexpression reduces the number of cells with aggregates (60% of cells without aggregates instead of 40%). Most strongly reduced is the number of cells with aggresomes, supporting their role in clearance of protein aggregates. In time-lapse microscopy we confirmed that aggregates disappear more often with Rab7 overexpression (17% instead of <5% of cells with aggregates). A reduction of alpha-synuclein by Rab7 was validated by analyzing alpha-synuclein content using immunoblots (40% reduction). Rab7 overexpression also reduced alpha-synuclein induced cell death as mesured by trypan blue staining. In a fly model of Parkinson's disease created by overexpressing alpha-synuclein in neurons, Rab7 rescued the locomotor deficit these flies display in the climbing assay. Taken together, Rab7 strongly increases cellular clearance of alpha-synclein aggregates, leads to fewer cells with aggregates, reduces alpha-synuclein amounts and toxicity, and is beneficial in a fly model of Parkinson's diseas. Activating Rab7 or its effectors could therefore be a new therapeutic strategy for Parkinson's disease.

Disclosures: B.H. Falkenburger: None. **E. Dinter:** None. **T. Saridaki:** None. **M. Nippold:** None. **L. Fensky:** None. **L. Diederichs:** None. **A. Voigt:** None. **J. Schulz:** None.

Poster

764. Neuroprotective Mechanisms in Parkinson's Disease

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 764.05/C19

Topic: C.03. Parkinson’s Disease

Title: Mesenchymal stem cells secretome and its role on brain repair effects on neurogenesis and Parkinson’s disease regeneration

Authors: *F. G. TEIXEIRA, SR[1], M. CARVALHO[2], S. SERRA[2], K. PANCHALINGAM[3], S. ANJO[4], B. MANADAS[4], L. PINTO[2], N. SOUSA[2], L. BEHIE[3], A. SALGADO[2];

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Abstract: It has been suggested that effects of MSCs in CNS regenerative medicine are mediated by their secretome. Indeed, our lab as previously shown that the secretome of MSCs from different sources increased neurogenesis and cell survival, inhibits apoptosis and has numerous neuroprotective actions in different pathological conditions. More recently, we have found that the use of dynamic culturing conditions, using computer-controlled bioreactors, can further modulate the MSC secretome thereby generating a more potent neurotrophic factor cocktail. Having this in mind, in this present work we aimed to (1) Perform a proteomic analysis of MSCs secretome, (2) assess the effects of MSCs secretome (in the form of conditioned media (CM)) on the proliferation, survival and differentiation of human neural progenitors (hNPCs) *in vitro* and *in vivo* on the resident cells of the dentate gyrus (DG) of adult rat hippocampus, and (3) Study the potential role of the sole use of the secretome as a therapeutic tool in Parkinson's Disease (PD) regenerative medicine. Results revealed that MSCs CM induced higher levels of neuronal differentiation (MAP-2+ and DCX+ positive cells) of hNPCs *in vitro*. *In vivo*, when injected into the DG of the hippocampus, was able to increase the levels of cell proliferation (Ki-67+ cells) as well as the number of newborn neurons (DCX+ cells) and astrocytes (GFAP+ cells). Additionally, when this MSC secretome was injected into a PD model, it was possible to observe that the secretome potentiated the recovery of dopaminergic neurons (increasing TH+ staining both in the SNc and Striatum), thereby leading to a recovery in the parkinsonian rats' motor performance outcomes. Finally, proteomic characterization of MSCs secretome (through LC-MS/MS and Bioplex assays) revealed the presence of important neuroregulatory molecules, namely PEDF, Cys C, GDN, Galectin-1, IGF-1 and GDNF. The present data shows the modulatory role of MSCs secretome in brain repair, further indicating that cell free therapies based in it could represent the basis of future strategies in PD regenerative medicine.

Disclosures: F.G. Teixeira: None. **M. Carvalho:** None. **S. Serra:** None. **K. Panchalingam:** None. **S. Anjo:** None. **B. Manadas:** None. **L. Pinto:** None. **N. Sousa:** None. **L. Behie:** None. **A. Salgado:** None.

Poster

764. Neuroprotective Mechanisms in Parkinson's Disease

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 764.06/C20

Topic: C.03. Parkinson's Disease

Title: NEDD4-mediated HSF1 degradation underlies α-synucleinopathy

Authors: *F.-F. LIAO[1], E. KIM[1,2], H. CAI[2];
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Abstract: Impairment of molecular chaperones and the ubiquitin ligases and proteasome system (UPS) have been implicated in several neurodegenerative diseases, including Alzheimer's (AD) and Parkinson's (PD), which are characterized by accumulation of abnormal protein aggregates. Induction of heat-shock proteins (HSP), such as via Hsp90 inhibition, is being investigated as a treatment option for these proteinopathic diseases, which depends on the activation of heat shock factor 1 (HSF1). Heat shock transcription factor 1 (HSF1), a master stress-protective transcription factor, activates genes encoding protein chaperones (e.g., iHsp70) and anti-apoptotic proteins. Compelling evidence suggests that increasing HSF1 activity may be a promising therapeutic approach for neurodegenerative diseases that are all characterized by protein misfolding and aggregation. Indeed, overexpression of iHsp70 or chronically activated HSF1 has been found to be beneficial in experimental models of all major neurodegenerative diseases. However, whether and how HSF1 is dysregulated during neurodegeneration has not been studied. HSF1 regulation is extremely complex, involving both transcription and posttranscription, as well as several posttranslational modifications (e.g., phosphorylation, acetylation, and sumoylation). It should be stressed that these regulatory mechanisms are studied almost exclusively in non-neuronal cell types (i.e., cancer). Aberrant accumulation of α-synuclein (α-syn)-positive Lewy bodies have been found in brains of AD and PD and are associated with accelerated cognitive dysfunction. In primary forebrain neuronal culture model, we discovered that mutant A53T α-syn induced drastic HSF1 protein degradation via UPS, which involves the HECT domain E3 ligase, Nedd4. Markedly reduced HSF1 was also found in the tyrosine hydroxylase (TH)-positive neurons in the substantia nigra (SNc) region of pre-symptomatic A53T α-syn transgenic mice. We found that Nedd4 can be transcriptionally upregulated by A53T α-syn and SIRT1 activity is tightly linked with the intracellular level of HSF1. Furthermore, the Lys 80 residue located in the DNA-binding domain of HSF1 is critical for the protein's stability which depends on its acetylation status and the interplay between acetylation and ubiquitination. Since we discovered HSF1 protein degradation in other proteinopathy conditions such as G93A SOD and mutant Htt, we speculate that HSF1 protein degradation, and perhaps its inactivation as a transcriptional factor (repression), represents a common molecular mechanism underlying neurodegeneration.

Disclosures: **F. Liao:** None. **E. Kim:** None. **H. Cai:** None.

Poster

764. Neuroprotective Mechanisms in Parkinson's Disease

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 764.07/C21

Topic: C.03. Parkinson's Disease

Support: CIHR

FRQ-S

Title: Roles of ERα, ERβ and GPER1 receptors in neuroprotective and anti-inflammatory effects of 17β-estradiol in the murine enteric system in a MPTP model of Parkinson's disease

Authors: A.-A. POIRIER[1], M. CÔTÉ[1], M. BOURQUE[1], M. MORISSETTE[1], T. DI PAOLO[1,3], *D. SOULET[2,4];
[1]CHUQ Res. Ctr., Quebec City, QC, Canada; [2]Neurosci., CHUQ Res. Ctr., Quebec, QC, Canada; [3]Laval University, Pharm. Fac., Quebec City, QC, Canada; [4]Psychiatry and Neurosci., Laval University, Med. Fac., Quebec City, QC, Canada

Abstract: Motor symptoms in Parkinson's disease (PD) are often preceded by non-motor symptoms related to dysfunctions of the autonomic nervous system such as constipation, defecatory problems and delayed gastric emptying. These gastrointestinal impairments are associated with the alteration of dopaminergic (DA) neurons in the myenteric plexus (MP) of the gut. Studies in our laboratory have demonstrated the immunomodulatory effect of female sex hormones to treat neurodegeneration in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of enteric nervous system degeneration in PD. We also uncovered the implication of the G protein-coupled estrogen receptor 1 (GPER1) in this phenomenon. In order to better understand the role of the estrogen receptors ERα, ERβ and GPER1 in neuroprotection and immune modulation in the MP, adult C57BL/6 male mice received, daily for 10 days, 2 injections of different combinations of the following products: 17β-estradiol (1 µg), G1 (5 µg) GPER1 agonist, G15 (10 µg) GPER1 antagonist, PPT (1 µg), ERα agonist, DPN (3 µg), ERβ agonist and ICI 182,780 (25µg) ERα/β antagonist. On day five, 4 injections of saline or MPTP (4.75 mg/kg) were administered. On day ten, mice were killed, the ileum was fixed and microdissected to isolate the MP. Cuprolinic blue staining and immunohistochemistry with antibodies against tyrosine hydroxylase (TH) and ionized calcium-binding adapter molecule 1 (Iba-1) were performed for stereological counting of total neurons, DA neurons (TH+) and macrophages (Iba-1+). We observed a loss of about 85% TH+ neurons in MPTP mice and maintenance of control levels following 17β-estradiol and G1 treatments, demonstrating the

important implication of GPER1. The ERα/β specific agonists, PPT and DPN, only partially prevented the DA loss resulting from MPTP intoxication. There was no difference in total neurons counts between groups, suggesting that neuronal loss was specific to TH+ neurons. Moreover, we observed an increase of approximately 55% in the number of macrophages in MPTP mice, but maintenance of control levels with 17β-estradiol and G1 treatments, demonstrating a significant anti-inflammatory effect of the drug in MPTP animals. When administered along with the antagonist G15, 17β-estradiol did not lower the number of macrophages, indicating the important implication of GPER1. Overall, the present results suggest that estrogen therapy may help prevent the loss of DA neurons and infiltration of macrophages in the MP in a MPTP mouse model of Parkinson's disease, mainly involving GPER1 and, to a lesser extent, ERα/β. This suggests a potential therapeutic avenue of immunomodulation for the human condition.

Disclosures: **A. Poirier:** None. **M. Côté:** None. **M. Bourque:** None. **M. Morissette:** None. **T. Di Paolo:** None. **D. Soulet:** A. Employment/Salary (full or part-time):; FRQ-S. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; CIHR.

Poster

764. Neuroprotective Mechanisms in Parkinson's Disease

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 764.08/C22

Topic: C.03. Parkinson's Disease

Support: Regione Emilia-Romagna and Region Aquitaine

Title: Endogenous Nociceptin/Orphanin FQ is neurotoxic for nigral dopamine neurons

Authors: *L. ARCURI[1], S. BIDO[1], R. VIARO[2], F. LONGO[1], M. CALCAGNO[1], P.-O. FERNAGUT[3], G. CALÒ[1], E. BEZARD[3], M. MORARI[1];
[1]Med. Sci., [2]Biomed. and Specialty Surgical Sci., Univ. of Ferrara, Ferrara, Italy; [3]Inst. des Maladies Neurodégénératives, Univ. de Bordeaux, Bordeaux, France

Abstract: Indirect evidence that nociceptin/orphanin FQ (N/OFQ) and its receptor (NOP) might contribute to the degeneration of nigral dopamine (DA) neurons associated with experimental parkinsonism has been presented. Indeed, N/OFQ knockout mice were found to be partially resistant to the neurotoxic effect of MPTP (Marti et al, J Neurosci 25: 9591, 2005). However,

N/OFQ is obtained by cleavage of a larger precursor, which codes for other two peptides, namely nocistatin and N/OFQ II, which might also play a role in MPTP-induced neurodegeneration. Therefore, to unequivocally prove the neurotoxic role of N/OFQ we undertook a genetic and pharmacological approach, using NOP receptor knockout (NOP-/-) mice, and the small molecule NOP-selective receptor antagonist SB-612111. Stereological unbiased methods were used to estimate the total number of DA neurons in acute (4x25 mg/Kg, i.p., 90 min apart) and subacute (25 mg/Kg, i.p., once daily for 7 days) MPTP mouse models of PD. NOP-/- mice showed a 50% greater amount of nigral DA neurons spared in response to acute MPTP compared to controls. Consistently, SB-612111, administered (10 mg/Kg, twice daily, i.p.) from 4 days before the onset of MPTP treatment, and for additional 6 days (10 days overall) prevented the loss of nigral DA neurons and DA axonal terminals in the striatum caused by subacute MPTP in naïve mice. To investigate whether N/OFQ is directly neurotoxic to DA neurons, we cultured SH-SY5Y cells in the presence of 6-OHDA and N/OFQ or the selective NOP receptor agonist UFP-112. 6-OHDA showed a strong neurotoxic effect on cell viability, which was exacerbated by N/OFQ and UFP-112. Two NOP receptor antagonists (UFP-101 and SB-612111) prevented the effect of UFP-112, confirming that this effect was mediated by the NOP receptor. These results show that endogenous N/OFQ contributes to DA neuron loss associated with MPTP treatment in mice, suggesting that NOP receptor antagonists might have neuroprotective potential. A study testing SB-612111 in the synuclein-AAV rat model is ongoing, to more convincingly prove that endogenous N/OFQ contributes to neurodegeneration associated with Parkinson's disease.

Disclosures: L. Arcuri: None. **S. Bido:** None. **R. Viaro:** None. **F. Longo:** None. **M. Calcagno:** None. **P. Fernagut:** None. **G. Calò:** None. **E. Bezard:** None. **M. Morari:** None.

Poster

764. Neuroprotective Mechanisms in Parkinson's Disease

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: C.03. Parkinson's Disease

Support: NIH Grant NS070825

Title: Exercise promotes alterations in Hif1a and Hif2a levels in the SN, which play different roles in the survival of DA neurons in exercise (Hif1a) and standard (Hif2a) conditions

Authors: M. SMEYNE, Y. JIAO, L. OAKLEY, *R. J. SMEYNE;
Dept Dev Neurobiol, St. Jude Children's Res. Hosp., Memphis, TN

Abstract: Neuroprotection in the brain, and specifically the substantia nigra pars compacta (SNpc), is likely the result of the combination of a number of factors whose end result is the maintenance of metabolic and oxidative homeostasis. Exercise reduces the risk of developing disorders such as Parkinson's disease (PD), Alzheimer's disease and stroke, as well as providing neuroprotection in experimental models of these disorders. Voluntary wheel running provides partial to full protection to dopaminergic (DA) neurons of the SNpc in a mouse model of parkinsonism, dependent on both the number of daily wheel revolutions and length of time which they run. The role of the transcription factor hypoxia inducible factor (HIF) in this exercise-induced neuroprotection has been investigated. HIF is important in sensing cellular oxygen levels and initiating adaptive mechanisms in the event of hypoxia or oxidative stress. HIF functions as a heterodimer consisting of an inducible isoform (HIF1a, HIF2a, HIF3a) and a constitutive isoform (HIF1b, identical to the aryl hydrocarbon receptor nuclear translocator (ARNT)). Hif1a induces genes encoding proteins known to be important in the regulation of metabolism, autophagy, erythropoiesis, and vascular development and angiogenesis. Hif2a (Epas1) is necessary for mitochondrial homeostasis, expression of antioxidant enzymes, control of tyrosine hydroxylase expression, and vascular remodeling. Acute hypoxia induces increased HIF 1a in the brain, but with chronic exposure to low oxygen HIF levels return to baseline. We have previously reported that running exercise induces hypoxia in DA neurons as well as the modulation of Hif1a and Epas1 expression. Additionally, reduction of Hif1a or Epas1 in postnatal neurons has differential effects on DA neuron number in the SNpc. Conditional knockout (CKO) of Hif1a results in lower DA neuron number with exercise or exercise plus 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment, while Epas1 CKO mice show lower DA neuron number in standard housing conditions (SH) that is rescued with 3 months of exercise. The downstream signaling regulated by Hif1a and Epas1 in exercise and standard conditions is currently being explored to gain further understanding of the roles of Hif1a and Epas1 in the survival and maintenance of SNpc DA neurons.

Disclosures: **M. Smeyne:** None. **Y. Jiao:** None. **L. Oakley:** None. **R.J. Smeyne:** None.

Poster

764. Neuroprotective Mechanisms in Parkinson's Disease

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Program#/Poster#: 764.10/C24

Topic: C.03. Parkinson's Disease

Title: The role of cerebral dopamine neurotrophic factor in zebrafish

Authors: *Y.-C. CHEN, S. SEMENOVA, P. PANULA;
Univ. of Helsinki, Helsinki, Finland

Abstract: Cerebral dopamine neurotrophic factor (CDNF) with potential therapeutic applications for the treatment of Parkinson's disease (PD) belongs to the evolutionary-conserved novel CDNF/ MANF family. CDNF not only restores the loss of dopaminergic neurons in PD animal models, but also protects cortical neurons against ischemic stroke. However, the molecular mechanisms of CDNF during development or disease pathology are still largely unfolded. In this study, using zebrafish we report that cdnf mRNA was mainly found in brain, myotomes and ears during embryonic development by *in situ* hybridization and detectable in adult organs including the brain, eyes, kidney and liver by qPCR. We also generated two cdnf -knockout fish strains with a one-nucleotide insertion and a sixteen-nucleotide deletion on exon 2 of cdnf gene by the CRISPR/Cas9 method. These indel mutations introduced a premature stop codon causing malfunctioned proteins. The larval cdnf -/- mutants did not show apparent gross phenotype nor was the locomotor behavior impaired although a significant reduction of cdnf mRNA was detected in cdnf +/- and cdnf -/- larvae in comparison of wild-type siblings. Notably, a dramatic increase of the tyrosine hydroxylase 2 transcripts, one of the teleost counterparts of mammalian tyrosine hydroxylase, was discovered when larvae lacked cdnf expression. Notch1a, tyrosine hydroxylase 1 and histidine decarboxylase transcripts showed no significant changes. The new zebrafish genetic models, cdnf -/- mutants may provide a powerful tool for understanding the biological functions of this neurotrophic factor.

Disclosures: Y. Chen: None. **S. Semenova:** None. **P. Panula:** None.

Poster

764. Neuroprotective Mechanisms in Parkinson's Disease

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Topic: C.03. Parkinson's Disease

Support: The study was funded by the Boehringer Ingelheim Ulm University BioCenter (BIU)

Title: Neuroprotective effects of monoacylglycerol lipase inhibition in a 6-hydroxydopamine model of Parkinson's disease in mice

Authors: *C. PORAZIK[1,2], J. HANSELMANN[2], N. PASQUARELLI[1,2], A. WITTING[2], B. FERGER[1];

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Abstract: Monoacylglycerol lipase (MAGL) is the principal enzyme for 2-arachidonylglycerol (2-AG) metabolism and an important player in the endocannabinoid system. Here, we investigate the effects of two commercially available MAGL inhibitors KML29 and JZL184 in comparison with the cyclooxygenase 2 (COX2) inhibitor rofecoxib in an animal model of Parkinson's disease (PD) 6-Hydroxydopamine (6-OHDA) (3.5 µg/1 µl) was administered in the left striatum in male C57BL/6JRj mice. KML29, JZL184 and rofecoxib (30 mg/kg/day p.o.) were administered daily for one week starting one day before 6-OHDA surgery. Rotarod measurement was performed at day 7. Post mortem, striatal dopamine depletion and nigral tyrosine hydroxylase positive (TH+) cell loss were evaluated. Furthermore, the effect of MAGL inhibition on mechanistic biomarkers was assessed. 6-OHDA led to a 70 % dopamine depletion in the striatum and 40% loss of TH + neurons in the substantia nigra. The neuroprotective effect of KML29 was indicated by attenuation of dopamine depletion by 50 % and TH+ neuron loss by 30 %. Motor behavior was impaired by 6-OHDA but not restored by MAGL inhibition. Overall, the effects of JZL184 and rofecoxib treatment were less pronounced. The MAGL inhibitors increased 2-AG levels and decreased arachidonic acid and prostaglandins in the brain. Rofecoxib was able to decrease prostaglandins but had no effect on 2-AG and arachidonic acid levels. In conclusion, administration of the MAGL inhibitor KML29 further strengthens the concept of targeting the endocannabinoid system as a valuable therapeutic concept in PD.

Disclosures: C. Porazik: None. **J. Hanselmann:** None. **N. Pasquarelli:** None. **A. Witting:** None. **B. Ferger:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co KG.

Poster

764. Neuroprotective Mechanisms in Parkinson's Disease

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CONACyT scholarship 361288

Title: Intramuscular administration of C-terminal fragment of tetanus toxin modulates Nrf2 expression and prevents locomotor damage in rats with MPP+

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Abstract: Parkinson's disease has been linked to different celular mechanisms which of them, produce neurodegeneration in the substancia nigra pars compacta (SNpc). Mainly, deregulation of protein control, excitotoxicity, mitochondrial deficit and oxidative stress are common markers and have been proposed like triggers of celular death. However, oxidative stress (OS) is one of the most prevalent events and its regulation, has been demonstrated could prevent the celular damage. So far, the intracelular regulation of OS has been characterised trough by Nrf2 transcription factor, which lead to synthesis of antioxidant and trophic proteins. Since there, the use of molecules which activate Nrf2 have been a new target for models of neuroprotection. Neurotrophins, can activate MAPK/IP3K pathway which could lead to Nrf2 activation and in our laboratory we have used a molecule like-neurotrophin, it is the case of C-terminal fragment of tetanus toxin that has been demonstrated prevents the damage in hemiparkinsonian rats. The aim of this work, was evaluated the effect of the administration of C-terminal fragment of tetanus toxin about Nrf2 expression in rats with MPP+ and a possible effect overt the motor asymmetry. Male Wistar rats were used and 3 previous days to stereotaxical surgery were administrated with Hc-TeTx (20 μg/kg) or vehicle intramuscular via. One day before of surgery, one group of animals were evaluated in cylinder test and after, that animals were evaluated 3 days posterior to surgery and other group of animals were euthanised at the same time, to evaluated Nrf2, 3-NT and tyrosine hydroxilase (TH) expression trough immunohistochemistry. Results shown that the rats administrated with Hc-TeTx previous to MPP+ deposition, prevents the locomotor activity asymmetry respect to rats only with MPP+. In the case of immunohistochemistry, Hc-TeTx caused that loss of TH in SNpc of rats were lesser than the the MPP+ group, besides the nitration of proteins has a different pattern of expression with a probable effect of anti apoptotic and a positive regulation of OS. Finally, 3 days after of the MPP+ lesion, the Nrf2 expression in rats with Hc-TeTx decreased the levels of this protein in SNpc, the correlation between the potential positive locomotor effect, probably is due a regulation of Nrf2, because although the MPP+ increased Nrf2 expression, the locomotor activity was impaired whereas Hc-TeTx improves the behaviour. In conclusion Hc-TeTx could act as protective molecule that modulates OS trough Nrf2 expression in the model of dopaminergic lesion with MPP+.

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Poster

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Support: NIH/NINDS 1F31NS084722-01A1

Title: Role of microRNA-155 in alpha-synuclein induced inflammatory response in a model of Parkinson's disease

Authors: *A. D. THOME, A. S. HARMS, L. A. VOLPICELLI-DALEY, D. G. STANDAERT; Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: Parkinson disease (PD) is a neurodegenerative disorder characterized by loss of dopamine neurons in the substantia nigra pars compacta (SNpc) and aggregates of the protein alpha-synuclein (α-syn). Increasing evidence points to inflammation as a chief mediator of injury, however the role of α-syn in triggering and sustaining this inflammation remains unknown. Neuro-inflammatory responses have shown to be dynamically regulated by short, non-coding sequences called microRNAs (miRs). MiRs regulate messenger RNAs in a post-transcriptional fashion by binding to specific 3' untranslated regions resulting in repression or degradation of the transcript. We used an *in vivo* mouse model in which human α-syn is overexpressed by an AAV2 viral vector in mice (AAV2-SYN), resulting in elevated cytokine expression, reactive microgliosis, and progressive dopamine cell loss. At two weeks and four weeks after SNc AAV injection, we isolated miRNAs from the substantia nigra (injected and contralateral sides) and studied miRNA expression using a Qiagen PCR array containing probes for 84 microRNAs involved in either pro-inflammatory or anti-inflammatory regulation. We found that four of the microRNAs showed enhanced expression and two were reduced at two weeks post transduction. Among those which were increased was miR-155, which has been previously identified in other neurodegenerative diseases such as multiple sclerosis, amyotrophic lateral sclerosis, and Alzheimer disease. MiR-155 is known to target inflammatory pathways to up-regulate IL-1, IL-6, and TNF-α and regulates anti-inflammatory pathways in reducing IL-10, Arg 1, IL-13R, and TGF-βR pathway proteins. We confirmed the increase in miR-155 using qPCR, which demonstrated a 1.55 ± 0.09 ($p=0.01$) fold increase of miRNA-155 at 2 weeks post transduction and a trend toward increase at 4 weeks (1.28 ± 0.28). In 4 week mouse brain tissue, we observed decreases in MHCII expression and IgG deposition in miR-155 knockout mice compared to their WT counterparts in the SNpc. We hypothesize that this enhanced miR-155 expression promotes and sustains the inflammatory environment associated with over-expression of human α-syn which eventually leads to dopaminergic cell loss in the SNpc. These data and future experiments may point to microRNA-155 as a target for novel therapeutic treatments for

PD. Supported by APDA Advanced Center for PD Research at UAB, the Parkinson Association of Alabama, and NINDS 1F31NS084722-01A1.

Disclosures: **A.D. Thome:** None. **A.S. Harms:** None. **L.A. Volpicelli-Daley:** None. **D.G. Standaert:** None.

Poster

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PAR fore Parkinson

National Parkinson Foundation CSRA

Title: Nrf2-mediated neuroprotective mechanisms of Dimethylfumarate in a mouse model of Parkinson's disease

Authors: ***M. AHUJA**[1], N.-A. KAIDERY[1], L. YANG[1,3], N. CALINGASAN[4], N. SMIRNOVA[5], A. GAYSIN[6], I. GAYSINA[7], T. IWAWAKI[8], J. MORGAN[2], R. RATAN[5], I. GAZARYAN[5], A. STARKOV[4], F. BEAL[4], B. THOMAS[1,2];
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Abstract: Augmentation of cellular antioxidant capacity either by pro¬viding exogenous anti¬oxidants or by enhancing it endo¬genously has been the most in¬tensely in¬ves¬tigated approach in Parkinson's disease (PD) therapies. One of the strategies involves activating the nuclear-factor-E2-related factor 2 (Nrf2)/anti¬oxidant re¬sponse element (ARE) sig¬nal¬ing pathway, which regu¬lates ex-pression of anti-oxi¬dative, anti-in¬flam¬matory, and cyto¬pro¬tective genes. Tecfidera is an oral formulation of dimethyl¬fumarate (DMF) that is currently approved in USA as a treatment for Multiple sclerosis. Fumaric acid esters such as dimethyl and mono-methyl ¬fumarate (DMF and MMF) have been shown to exert

neuro¬pro¬tective effects by activating the Nrf2/ARE sig¬nal¬ing pathway. In this study we investigated *in vivo* pharma¬cokinetics of DMF and its mode of action to block 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) toxicity, as¬so¬ci¬ated oxi¬dative damage, neuroin¬flam¬mation and mitochondrial dysfunction in mice. We found that administration of dimethylfumarate and its active metabolite mono-methyl¬fumarate activates Nrf2 pathway *in vitro* using Neh2-luciferase reporter, and when orally administered in an OKD48-luciferase transgenic mice *in vivo*. Both dimethyl and mono-methyl¬fumarate at (10, 25, 50, and 100mg/kg) exhibited dose de¬pen¬dent neuroprotective effect against acute MPTP neuro-toxicity assessed by stereological cell counts of total and tyrosine hydroxy¬lase positive neu¬rons in sub¬stanti¬a nigra and by measuring striatal levels of catecholamines in wild type but not in Nrf2 null mice. Dimethyl¬fumarate prevented MPTP-induced oxi¬dative damage and inflammation assessed by 3-nitrotyrosine content, CD68 immuno¬reactivity and ex¬pression of pro-in¬flam¬matory cyto¬kines respectively in the ventral midbrains. Both dimethyl and mono-methylfumarate increased mRNA of nuclear and mitochondrial genes associated with mitochondrial function in wild type mouse embryonic fibroblasts (MEFs) but not in Nrf2 null MEFs. Our results suggest that fumaric acid esters exhibit neuroprotective effect against nigrostriatal dopaminergic neuro-toxicity owing to their Nrf2 dependent anti-oxidant, and anti-inflammatory activity and by facilitating mitochondrial biogenesis. Given that oxidative damage, neuroinflammation and mitochondrial dysfunction are all implicated in PD pathogenesis, our results provide strong pre-clinical evidence in favor of repurposing dimethylfumarate as a novel PD therapeutic.

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Poster

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Topic: C.03. Parkinson’s Disease

Support: NIH 1RO1 NS065338-01A2

Title: Temporal dynamics of 20S and 26S proteasome activities in brain regions containing differentially susceptible central dopaminergic neurons following acute neurotoxicant administration

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Abstract: Parkinson disease is a chronic neurodegenerative disease characterized by significant loss of nigrostriatal dopamine (NSDA) neurons. While NSDA neurons originating in the substantia nigra (SN) are susceptible to degeneration, tuberoinfundibular dopamine (TIDA) neurons in the arcuate nucleus (ARC) are spared. This pattern of DA neuronal susceptibility can be simulated following exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). MPTP inhibits mitochondrial complex I resulting in the generation of protein damaging reactive oxygen species. Oxidative damage to proteins can produce conformational changes which may result in alteration of native protein function and toxic aggregate formation. The proteasome is a highly dynamic complex that exists in an equilibrium between the 20S and 26S catalytically active forms. Degradation of oxidatively damaged proteins occurs primarily through a ubiquitin- and ATP-independent mechanism involving the more abundant 20S core proteasome particle. The 26S proteasome is composed of the 20S catalytic core and 19S regulatory subunits, and specifically degrades ubiquitinated proteins in an ATP-dependent mechanism. The purpose of this study was to characterize the time course effects of MPTP on 20S and 26S proteasome activities in brain regions containing axon terminals of NSDA (striatum; ST) and TIDA (median eminence; ME) neurons. The underlying hypothesis of this study is that differences in 20S/26S proteasome dynamics may underlie susceptibility of these DA neurons to toxicant exposure. Proteasome activity was measured using chymotryptic-like substrate (Suc-LLVY-AMC) in tissue collected 4, 6, 8, 12 or 24 h after MPTP (20 mg/kg; sc) or vehicle. 26S Proteasome activity in ST synaptosomes was increased 4 h after MPTP and then diminished over time, whereas 20S proteasome activity decreased 4 h following MPTP and then increased over time. In congruence with enhanced 26S activity, expression of the catalytic β5 subunit in the SN was significantly increased after MPTP exposure. In contrast, 26S proteasome activity in the ME was not altered either 4 or 24 h following MPTP. The maintenance of 26S activity in the ME correlated with an increase in expression of β5 catalytic subunit in the ARC after MPTP. Differential proteasome dynamics between the ST and ME following neurotoxicant exposure suggests that effective modulation of the proteasome may be a determining factor in the susceptibility of central DA neurons to acute toxicant exposure.

Disclosures: T. Lansdell: None. **K.J. Lookingland:** None. **J.L. Goudreau:** None.

Poster

764. Neuroprotective Mechanisms in Parkinson's Disease

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Topic: C.03. Parkinson's Disease

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Conacyt Grand FOMIX 224038

Title: Hydroxytyrosol inhibits MAO-B and improves dopaminergic functional recovery after MPP+ administration in rats

Authors: *G. A. PÉREZ-BARRÓN[1], A. MONROY-NOYOLA[1], M. RUBIO-OSORNIO[2], S. MONTES[2], S. GARCÍA-JIMENEZ[1];
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Abstract: Parkinson's disease is a neurological syndrome of unknown etiology, environmental organic molecules such as the metabolite 1-methyl-4-phenylpyridinium (MPP+) which induce a selective toxicity towards dopaminergic neurons in the nigrostriatal pathway. Another hypothesis in this disease is the loss of dopaminergic neurons by an increase in the catabolism of dopamine across the monoamine oxidase (MAO) enzyme that produced reactive oxidant species. *In vivo* studies have demonstrated that hydroxytyrosol (HT) is a potent antioxidant in the central nervous system. In the present study, Wistar male rats were administered a single dose of 1.5 mg/Kg of HT intravenously. Five minutes later, the animals received a intrastriatal stereotaxic micro-injection of 10 µg MPP+ dissolved in 8µL of sterile saline solution. Six days later, all animals were treated with apomorfine at a dose of 1 mg/Kg by subcutaneous injection for the behavioral evaluation through counting ipsilateral rotations during 1 hour. Rats were sacrificed by decapitation and the striatum region was dissected for the quantification of catecholamines and MAO activities. The results show that pretreatment with HT diminished significantly ($p< 0.05$) the number of ipsilateral rotations (70%). This behavioral recovery was corroborated by the 78% preservation of the levels of striatal dopamine ($p < 0.05$) and an inhibition of 20% and 60% of the MAO-A and B activity respectively ($p < 0.05$). These results demonstrate the neuroprotective effect of HT in the MPP+ Parkinson´s disease model in rats, possibly due to the inhibition of MAO-B meanly.

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Poster

764. Neuroprotective Mechanisms in Parkinson's Disease

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Topic: C.03. Parkinson's Disease

Title: Comparative effect of novel incretin analogues in an *in vitro* model of Parkinson's disease

Authors: *J. JALEWA, M. K. SHARMA, C. HOLSCHER;
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Abstract: There is no viable treatment available for Parkinson's disease till date that could potentially prevent or treat this dreadful motor impairment disorder. Interestingly, several Exendin-4 (Byetta) studies have shown neuroprotective/neurorestorative properties in the pre-clinical and clinical studies of Parkinson's disease. Incretin hormone analogues were originally developed to treat type 2 diabetes, but recent research have shown their neuroprotective properties. Incretins can cross blood brain barrier and activate neurogenesis and synaptogenesis and growth factor signalling in neurons in the CNS. A range of novel long-lasting analogues for glucagon-like-peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) that are resistant to protease cleavage have been developed, which exhibit superior receptor activation properties, elongated half-life and are protected from renal clearance due to the acetylation that helps bind to the blood proteins. We have previously shown very promising effect of Liraglutide (Victoza) on SH-SY5Y cells against methyl glyoxal oxidative stress. In this study, we tested novel incretin analogues on the dopaminergic SH-SY5Y neuroblastoma cells against mitochondrial complex I inhibitor, Rotenone (a pesticide) toxicity. Here, we report for the first time comparative effect of six different incretin analogues (Liraglutide, Oxyntomodulin, Dual agonist, dAla-2GIP Glupal, Val-8 GLP-1 Glupal and Exenatide. Post-treatment with 1nM, 10nM and 100nM incretin analogues for 12hrs increased the cell viability (XTT assay) of SH-SY5Y cells when tested against 1μM and 10μM Rotenone stress for 12hrs. In addition, the involvement of PI3K signalling in the comparative neuroprotective effect of these incretin analogues will be detailed. Further results will be unrevealed at the meeting.

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Poster

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Topic: C.03. Parkinson's Disease

Support: MJFF foundation

Title: Neuroprotective effect of 4R, a tobacco cembranoid on 6-hydroxydopamine-induced Parkinson's disease in rat

Authors: *J. HAO[1], J. HU[1], P. A. FERCHMIN[2], V. A. ETEROVIC[2];
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Abstract: The *in vivo* experiments of the present study have shown that (1*S*,2*E*,4*R*,6*R*,-7*E*,11*E*)-2,7,11-cembratriene-4,6-diol (4R), a cyclic diterpenoid found in leaves of *Nicotiana* species, decreased the depletion of tyrosine hydroxylase (TH) positive cells in striatum and substantia nigra (SN) in 6-OHDA-induced PD model in rat. Compared to the contralateral side, there was a significant depletion of TH-positive cells in the right (the lesion) side of striatum and right side of substantia nigra (SN). In the vehicle (DMSO) controls, the TH density was 51.9%±5.7 and 23.6%±14.7 of the density observed in the left not lesion contralateral. However, 6 or 12 mg/kg 4R significantly mitigated TH depletion in both striatum and SN in the lesion side. TH expression was 70.3±11.3% and 62.8±25.8% of the left, not lesion side striatum and SN respectively after 6mg/kg 4R treatment. TH expression was 80.1±11% and 79.3±15% of the control side striatum and SN respectively after 12mg/kg 4R treatment. The behavioral deficit was significantly improved after 4R treatment as shown by the performance in the cylinder test and corner test. The 4R-injected subjects were approaching the expected baseline score of 0.5. The scores of the corner test were 0.63, 0.62, 0.51, 0.50 in the 6 mg/kg 4R-treatment groups at 1, 2, 3 and 4 weeks after the injection of 6-OHDA respectively. The scores of the DMSO group they were 0.69, 0.8, 0.81, 0.87 at 1, 2, 3 and 4 weeks after the injection of 6-OHDA respectively. The scores of the cylinder test were 0.48, 0.46, 0.47, 0.49 in the 6 mg/kg 4R-treatment groups at 1, 2, 3 and 4 weeks after the injection of 6-OHDA respectively. In contrast, the scores of the DMSO were 0.36, 0.31, 0.22, 0.22 in DMSO groups at 1, 2, 3 and 4 weeks after injection of 6-OHDA respectively. Similar results were observed in the 12mg/kg 4R-treatment groups. *In vitro* 4R protected the differentiated neuro-2a cells (a neuronal cell line) from 6-OHDA-induced cytotoxicity, and this protection was associated with restoration of the anti-apoptotic proteins, p-Akt and Hax-1, expression and decrease of the cellular levels of cleaved caspase-3. Furthermore, 4R also inhibited inflammatory responses in brain-derived endothelial cells induced by TNF-α, which were shown to reduced the level of p65, a NF-kB subunit, VACM-1 expression, and the percentage of monocytes adhered to endothelial cells. In conclusion, the present study demonstrates that 4R has a protective effect on 6-OHDA-induced PD model in rat. In addition,

4R inhibited inflammation and restored Akt and Hax-1 functions, which are most likely involved in the mechanisms of 4R protection against 6-OHDA-induced injury.

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Poster

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Topic: C.03. Parkinson's Disease

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Title: Substantia nigra activation as a mechanism of neuroprotection in a progressive mouse model of Parkinson's disease

Authors: *R. HOOD[1], C. MOORE[2], P. M. FULLER[3], C. K. MESHUL[1,2];
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Abstract: Parkinson's disease (PD) is a common neurodegenerative disorder, affecting 7-10 million people worldwide. Through a progressive loss of dopaminergic cells in the substantia nigra pars compacta (SNpc), signaling in the basal ganglia becomes dysfunctional, leading to declining motor and cognitive function. Targeting specific dysregulated regions in the basal ganglia may help to potentially protect SNpc cells from further loss. Imaging studies of PD patients demonstrate an alteration in motor cortex (MC) activation when compared to healthy control patients, and repetitive transcranial magnetic stimulation targeting the MC attenuates motor impairments in PD patients. These results suggest the MC is viable as a novel therapeutic target. We have previously shown that unilateral Vgat (the gene encoding the vesicular GABA transporter VGAT) deletion in the MC of Vgatflox/flox mice injected with AAV-Cre-GFP is completely bilaterally protective against a progressive PD model utilizing 4 weeks of an increasing dose of 1-methyl-2-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 5 d/wk injected i.p., at doses of 8, 16, 24, and 32 mg/kg/d. Since VGAT is required for GABAergic function, we believe targeting GABAergic interneurons with focal AAV-Cre-GFP injections prevents inhibitory GABAergic signaling in the MC, and this disinhibtion exerts a neuroprotective effect in our model. What is not known, however, is the mechanism by which this neuroprotection occurs. Since the MC strongly innervates the dopamine-depleted striatum, we hypothesized that MC disinhibition would activate the corticostriatal pathway. Based on post-embed immunogold

labeling for glutamate, there is no detectable change in glutamate in striatal nerve terminals originating from the cortex either after MPTP or in Cre-injected Vgatflox/flox animals. Therefore, though the majority of MC projections are corticostriatal projections, we believe the mechanism of protection is not through activation of the corticostriatal pathway. Cytochrome oxidase (CO) was used as a marker of cellular activity and showed no significant difference in labeling between any treatment groups in the striatum. However, CO labeling in the SN was significantly decreased in wt mice given MPTP, and this decrease was attenuated in the Vgatflox/flox+MPTP mice. It is possible that the mechanism of protection occurs through activation of the SN. Anterograde labeling studies reveal bilateral projections from the motor cortex to both the STN and the SN, suggesting that the hyperdirect pathway may indirectly be activating the SN, or the corticonigral pathway could be directly activated, leading to protection from MPTP lesions.

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Poster

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Title: Inactivation of calcineurin/cyclophilin D by Cyclosporin A as a neurorestorative target in a progressive MPTP animal model of PD

Authors: M. J. CHURCHILL[1], M. D. SCONCE[1], C. MOORE[1], M. DECRESSAC[2], *C. K. MESHUL[1,3];
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Abstract: In Parkinson’s disease (PD), there is an increased inflammatory response as the disease progresses (Tufekci et al., 2012). The focus on targeting the inflammatory response has been the use of non-steroidal anti-inflammatory drugs; however, meta-analyses have shown inconclusive results (Samii et al., 2012). Animal data in a PD model suggests that cyclosporin A (CsA) has neuroprotective properties (Matsuura et al., 1999). In a human clinical fetal transplant study, when cyclosporin A was withdrawn from treatment, the UPDRS score increased (Olanow et al., 2003). CsA has two targets which are calcineurin, a regulator of inflammatory proteins and

the mitochondrial pore modulator, cyclophilin D. Specifically the focus of the effects of CsA upon calcineurin/cyclophilin were examined in the nigrostriatal dopamine (DA) pathway. CsA is first and foremost an anti-inflammatory drug as it inactivates calcineurin, preventing dephosphorylation of nuclear factor of activated T-cells (NFAT) and preventing component 3 of NFAT (i.e., NFATc3) from starting transcription of pro-inflammatory proteins, such as interleukin 2. A second target of CsA is cyclophilin D, which regulates the opening of the mitochondrial permeability transition pore (Doczi et al., 2011) preventing the release of cytochrome C, and thereby blocking apoptosis. We have developed a model of progressive loss of nigrostriatal DA over a 4-week time period by increasing the weekly dosing of MPTP (Goldberg et al., 2011), resulting in a 50-70% loss of DA. Using a more clinically relevant neurorestoration animal model of PD, CsA treatment (20 mg/kg/d, 7d/wk) was initiated following the 4 weeks of MPTP administration. Motor/strength testing revealed a significant 16% increase in grip strength, (i.e., unable to release from the bar) following MPTP ($p = .0004$), which was restored back to the control levels by CsA treatment. There was a 60% loss of tyrosine hydroxylase (TH) expression within the dorsal lateral striatum following MPTP, which recovered to only a 30% loss with CsA treatment. After MPTP, there was a 47% decrease in the number of TH-labeled neurons within the substantia nigra pars compacta compared to the controls, while CsA treatment resulted in only a 39% loss of TH-labeled neurons. Within the striatum, there was a significant increase of nearly 200% in the levels of SCG 10 (indicative of regenerating axons) in the MPTP/CsA group compared to the MPTP only ($p = .01$) and the vehicle group ($p = .008$). Overall, using a neurorestoration model of PD, our data suggests that CsA facilitates sprouting of striatal axons, resulting in improved motor function.

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Poster

764. Neuroprotective Mechanisms in Parkinson's Disease

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Program#/Poster#: 764.21/C35

Topic: C.03. Parkinson’s Disease

Support: National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20892

Title: Inhibition of Cdk5/p25 hyperactivity by a truncated peptide (TP5), derived from P35, a Cdk5 activator, provides neuroprotection in the MPTP model of Parkinson's disease

Authors: *B. BALACHANDRAN KRISHNAMMA, N. D. AMIN, S. SKUNTZ, V. SHUKLA, J. STEINER, P. GRANT, H. C. PANT;
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Abstract: Parkinson's disease (PD) is a chronic neurodegenerative disorder characterized by the loss of dopamine neurons in the substantia nigra, decreased striatal dopamine levels, and consequent extrapyramidal motor dysfunction. Recent evidence indicates that cyclin-dependent kinase 5 (Cdk5) is inappropriately activated in several neurodegenerative conditions including PD. To date, strategies to inhibit Cdk5 activity have not been successful in selectively targeting aberrant activity without affecting normal Cdk5 activity. Previously, we reported that TP5 peptide has neuroprotective effects in animal models of Alzheimer's disease. Here, we show that TP5 selective inhibition of Cdk5/p25 hyperactivation *in vivo*, rescues nigrostriatal dopaminergic neurodegeneration caused in the MPTP induced animal model of PD. TP5 peptide treatment also blocked dopamine depletion in the striatum and improved in gait dysfunction after MPTP administration. The neuroprotective effect of TP5 peptide is also associated with marked reduction in neuroinflamation and apoptosis. The findings reported here showing selective inhibition of Cdk5/p25 hyperactivation by TP5 peptide, identify the kinase as a potential therapeutic target to reduce neurodegeneration in Parkinson's disease.

Disclosures: B. Balachandran Krishnamma: None. **N.D. Amin:** None. **S. Skuntz:** None. **V. Shukla:** None. **J. Steiner:** None. **P. Grant:** None. **H.C. Pant:** None.

Poster

764. Neuroprotective Mechanisms in Parkinson's Disease

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 764.22/C36

Topic: C.03. Parkinson's Disease

Support: Canadian Institutes of Health Research (CIHR) MOP-82692 to TDP

Title: Plasma and brain levels of several steroids following progesterone treatment in neuroprotection of MPTP-treated male mice

Authors: *M. BOURQUE[1], M. MORISSETTE[1], S. AL SWEIDI[1], D. CARUSO[2], R. C. MELCANGI[2], T. DI PAOLO[1,3];
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Abstract: Steroids exert neuroprotective effects and neurodegeneratives diseases affect the level of neuroactive steroids. However, little is know about the changes induced by neuroactive steroid treatment when neurons are damaged. The aim of this study was to measure and compare plasma and brain levels of several neuroactive steroids in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated male mice following neuroprotection with progesterone (PROG) treatment. Mice received 4 injections of MPTP (6.5 mg/kg) and were treated with progesterone (8 or 16 mg/kg) during 6 days. Data obtained showed that among pregnenolone, PROG and its derivatives, only dihydroprogesterone (DHP) and isopregnanolone were increased in plasma of MPTP-treated mice. PROG treatments showed in plasma a dose-dependent increase in PROG levels; assessment of PROG metabolites revealed that both doses of PROG administered decreased DHP levels as compared to MPTP mice, while only the highest dose of PROG decreased isopregnanolone levels. Tetrahydroprogesterone levels were not affected in MPTP-treated male mice, and with PROG treatment. In brain tissue, the levels of all these neuroactive steroids were unchanged in MPTP-treated male mice, however treatment with PROG at the highest dose increase pregnenolone, PROG, DHP, isopregnanolone and tetrahydroprogesterone levels. Interestingly, PROG treatment at 8 mg/kg decreased pregnenolone levels and increased PROG and tetrahydroprogesterone levels in brain tissue. Significant positive correlations were observed between plasma and brain levels of PROG and a significant negative correlation was found between plasma and brain levels of isopregnanolone. The levels of testosterone metabolites dihydrotestosterone (DHT), 3α-diol and 3β-diol were decreased in the plasma of MPTP-treated mice, while no change was observed for dehydroepiandrosterone (DHEA) and testosterone. By contrast, in brain tissue, only DHT levels were increased. Treatment with PROG at 8 mg/kg decreased brain levels of DHT as compared to MPTP mice, while after treatment with the highest dose, an increase was observed. Brain levels of DHEA and 3β-diol were not modified in MPTP-treated mice, but PROG treatment at a dose of 16 mg/kg decreased the levels of these two steroids. Significant positive correlations were observed between plasma and brain levels of DHEA, as well as between plasma and brain levels of testosterone; a significant negative correlation was found between plasma and brain DHT levels. Our results shown that changes in brain steroids levels following a neuroprotective PROG treatment do not necessarily reflected the changes observed in plasma levels.

Disclosures: **M. Bourque:** None. **M. Morissette:** None. **S. Al Sweidi:** None. **D. Caruso:** None. **R.C. Melcangi:** None. **T. Di Paolo:** None.

Poster

764. Neuroprotective Mechanisms in Parkinson's Disease

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 764.23/C37

Topic: C.03. Parkinson's Disease

Support: Canadian Institutes of Health Research MOP-82692

Parkinson Society Canada Scholarship

Title: Neurorescue effects of Progesterone on dopaminergic neurons in the MPTP mouse model of Parkinson's disease

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Abstract: Parkinson disease (PD) is a neurodegenerative disease characterized by a loss of dopaminergic neurons in the nigrostriatal pathway. Several studies have reported the neuroprotective effect of estradiol while the efficacy of the ovarian steroid progesterone to prevent the loss of dopaminergic neurons is less documented. Previous studies have shown that treatment with low dose of progesterone has neuroprotective effects on striatal dopamine (DA) in mice lesioned with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) when administered before the toxin. However, the rescue and restorative potentials of this compound on the integrity of dopaminergic neurons remains to be investigated. In this study, we hypothesized that brain DA can be restored by progesterone when administered 24 h or even 5 days after the lesion with MPTP. Male mice received 4 injections of MPTP (8 mg/kg) and were treated with progesterone (once daily at 8 mg/kg) 24 h or 5 days after the lesion with MPTP during 5 days. The striatal levels of DA and its metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were quantified by HPLC. Specific binding to the dopamine transporter (DAT) and vesicular monoamine transporter 2 (VMAT2) was measured by autoradiography. The MPTP lesion decreased striatal DA concentrations while serotonin concentrations remained unchanged. MPTP mice treated with progesterone 24 h after the lesion had higher concentrations of DA, DOPAC and HVA than vehicle-treated MPTP mice, whereas this effect was not observed in mice treated with progesterone 5 days after MPTP compared to the vehicle-treated MPTP mice. Progesterone administered 24 h after the lesion partially prevented the striatal increase of HVA/DA ratio induced by MPTP. Autoradiography of striatal DAT and VMAT2 showed that treatment with progesterone 24 h after MPTP decreased the effect of the toxin in the striatum while no protection was observed when progesterone was administered 5 days after the toxin. These results suggest that the ovarian steroid progesterone at the dose of 8 mg/kg has the capacity to promote the recovery of dopaminergic neurons when administered 24 h after the MPTP lesion in male mice whereas no restorative effect 5 days post lesion was observed.

Disclosures: **N. Litim:** None. **M. Morissette:** None. **T. Di Paolo:** None.

Poster

764. Neuroprotective Mechanisms in Parkinson's Disease

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 764.24/C38

Topic: C.03. Parkinson's Disease

Support: Graduate School of Michigan State University (NKP)

Michigan State Pearl J Aldrich Endowment in Aging Related Research (CES)

Mercy Health Saint Mary's (FPM)

Morris K. Udall Center of Excellence for Parkinson's Disease Research at Michigan State University NS058830 (TJC, CES, KSC, JWL)

Title: Impact of aging on recombinant adeno-associated and lentiviral vector-mediated transduction of the rat nigrostriatal and striatonigral system

Authors: *N. POLINSKI, L. CONGDON, L. FISCHER, F. P. MANFREDSSON, M. BENSKEY, C. J. KEMP, N. C. KUHN, A. COLE-STRAUSS, K. STEECE-COLLIER, K. L. PAUMIER, J. W. LIPTON, C. E. SORTWELL;
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Abstract: Clinical trials are currently examining the efficacy of viral vector-mediated gene delivery for treating age-related neurodegenerative diseases such as Parkinson's disease (PD). While viral vector strategies have been successful in preclinical studies, to date, human clinical trials have disappointed. This may be partially due to the fact that preclinical studies fail to account for aging as an important covariate even though aging is the primary risk factor for PD, with the majority of idiopathic cases occurring in people over the age of 65. Previously, we found that gene transfer utilizing recombinant adeno-associated virus serotype 2/5 (rAAV2/5) results in decreased transduction efficiency in the aged (20 month) rat nigrostriatal system as compared to the young adult (3 month) rat (PMID: 25457558). Specifically, injection of rAAV2/5 expressing green fluorescent protein (GFP) to the substantia nigra (SN) of aged rats resulted in: 1) ~60% fewer cells expressing detectable GFP, 2) ~50% less striatal protein, and 3) 4-fold lower mRNA expression than identical injections into the young adult rat SN. These results were generalizable over rat strain, duration of expression, and location sampled in the nigrostriatal system. In the present series of experiments, we investigated whether the phenomenon of deficient transduction in the aged nigrostriatal system is generalizable to other vector constructs and other circuitry. To examine this, we compared the transduction efficiency

of rAAV2/5, rAAV2/2, rAAV2/9, or lentivirus (LV) expressing GFP in young (3 month) or aged (20 month) male Fischer 344 rats following injections into either the SN or the striatum, the structure most often targeted in PD gene therapy clinical trials. Four weeks after injection in the SN, three of the four vector constructs (rAAV2/5, rAAV2/2, and LV) were less efficient in transducing the aged nigrostriatal system as assessed via GFP immunoassay in the striatum. In contrast, rAAV2/9 GFP injection into the SN resulted in equivalent protein expression in the striatum of young adult and aged rats. Similarly, four weeks following injection into the striatum, all three rAAV serotypes were deficient in transducing the striatonigral system as assessed via GFP immunoassay in the SN pars reticulata. These results demonstrate that the aged brain is less amenable to viral vector-mediated gene transfer. As aging-related deficits in transduction have the potential to impact current and future gene therapy trials, identification of the mechanism of the deficiency will be required for efficient protein delivery in future gene therapy clinical trials for age-related neurodegenerative diseases.

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Poster

764. Neuroprotective Mechanisms in Parkinson's Disease

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 764.25/C39

Topic: C.03. Parkinson’s Disease

Support: Korea Institute of Science and Technology

Title: Pharmacological rescue of Parkinson’s disease symptoms in *Drosophila* larvae

Authors: ***D. LEE**[1], E. PODOLSKY[2], J. BLOSSER[2];
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Abstract: Parkinson’s disease (PD) is a devastating motor system disorder. However, its treatments, including the ‘gold standard’ drug L-DOPA, remain inadequate. In order to advance PD treatments and understanding of the disease, it is necessary to develop a better animal model that is fast and sufficiently mimic the pathology of human PD. The fruit fly *Drosophila melanogaster* has been widely used as a model for human diseases including PD, primarily due to its genetic similarity with mammals and the sophisticate genetic tools available to study disease mechanisms as well as potential therapies. Prior studies have demonstrated *Drosophila*

larvae to be a useful PD model, showing two key features: locomotion deficits and loss of dopaminergic (DA) neurons (Varga et al, 2014). This larval model can also be very useful in quickly screening drugs as well as probing their mechanisms due to its rapid onset of PD symptoms, which takes less than 4 days. In this study, therefore, we have extended this model to screen and better understand PD treatments. Both genetic and neurotoxin PD models (i.e., α-Synuclein (A53T) and rotenone, respectively) were used to quantify the symptomatic improvement in locomotion speed, turning rate, and pause time after treatment with potential PD drugs. First, the fly larvae were exposed to L-DOPA to determine whether they show similar symptomatic relief. When L-DOPA (100μM) was added to the food, both α-Synuclein (A53T) and rotenone-treated larvae showed significant improvements in the locomotion, demonstrating the usefulness of the fly larval model to study the rescue of PD symptoms. The next goal was to demonstrate how this model could be used to test previously understudied new drugs. For this purpose, the citrus flavonoid nobiletin was chosen for its previously demonstrated potential therapeutic benefit in various neural diseases including PD (Yabuki et al., 2014). Nobiletin (10μM) effectively rescued motor deficits in two larval PD models. Further, it was found that nobiletin's rescue effects were achieved through activation of D2 autoreceptors as there was no rescue in the larvae expressing D2 receptor RNAi selectively in DA neurons. We are currently examining the number of DA neurons rescued by L-DOPA and nobiletin. Taken together, our fly larval PD model can be a very useful model to rapidly and more effectively screen potential PD drugs and also to study their rescue mechanisms.

Disclosures: D. Lee: None. **E. Podolsky:** None. **J. Blosser:** None.

Poster

765. Epilepsy Genetics and Seizure Dynamics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 765.01/C40

Topic: C.07. Epilepsy

Support: the Korean Health Technology Research and Development (R&D) Project, Ministry of Health & Welfare, Republic of Korea A121070, HI13C0208

the Brain Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, Information and Communication Technology (ICT) & Future Planning (2013M3C7A1056564)

Title: Brain somatic mutations in MTOR cause focal cortical dysplasia type II leading to intractable epilepsy

Authors: J. LIM[1], W.-I. KIM[1], H.-C. KANG[3], D. KIM[2], D. KIM[3], *J. LEE[1];
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Abstract: Focal cortical dysplasia type II (FCDII) is a sporadic developmental malformation of the cerebral cortex characterized by dysmorphic neurons, dyslamination and medically refractory epilepsy. It has been hypothesized that FCD is caused by somatic mutations in affected regions. Here, we used deep whole-exome sequencing (read depth, 412-668×) validated by site-specific amplicon sequencing (100-347,499×) in paired brain-blood DNA from four subjects with FCDII and uncovered a de novo brain somatic mutation, mechanistic target of rapamycin (MTOR) c.7280T>C (p.Leu2427Pro) in two subjects. Deep sequencing of the MTOR gene in an additional 73 subjects with FCDII using hybrid capture and PCR amplicon sequencing identified eight different somatic missense mutations found in multiple brain tissue samples of ten subjects. The identified mutations accounted for 15.6% of all subjects with FCDII studied (12 of 77). The identified mutations induced the hyperactivation of mTOR kinase. Focal cortical expression of mutant MTOR by *in utero* electroporation in mice was sufficient to disrupt neuronal migration and cause spontaneous seizures and cytomegalic neurons. Inhibition of mTOR with rapamycin suppressed cytomegalic neurons and epileptic seizures. This study provides, to our knowledge, the first evidence that brain somatic activating mutations in MTOR cause FCD and identifies mTOR as a treatment target for intractable epilepsy in FCD.

Disclosures: J. Lim: None. **W. Kim:** None. **H. Kang:** None. **D. Kim:** None. **D. Kim:** None. **J. Lee:** None.

Poster

765. Epilepsy Genetics and Seizure Dynamics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 765.02/C41

Topic: C.07. Epilepsy

Support: NIH RO1 NS 33300

Title: Characterization of de novo gabrg2 mutations associated with epileptic encephalopathies

Authors: *D. SHEN[1,2], C. HERNANDEZ[1], W. SHEN[1], N. HU[1], A. PODURI[5,6], B. SHIEDLEY[7], E. GOLDBERG[8,9], I. HELBIG[8,9], X. ORTIZ-GONZALEZ[10,9], J. LEMKE[11], E. MARSH[12,9], R. MACDONALD[1,3,4];
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Univ., Nashville, TN; [5]Neurol., Boston Children's Hosp., Boston, MA; [6]Neurol., Harvard Med. Sch., Boston, MA; [7]Neurol., Boston Children's Hosp., Boston, MA; [8]Neurol. and Pediatrics, Univ. of Pennsylvania, Philadelphia, PA; [9]the Children's Hosp. of Philadelphia, Philadelphia, PA; [10]Neurol. and Pediatrics, the Univ. of Pennsylvania, Philadelphia, PA; [11]Inst. of Human Genet., Univ. of Leipzig, Leipzig, Germany; [12]Neurol. and Pediatrics, Children's Hosp. of Philadelphia, Philadelphia, PA

Abstract: Epileptic encephalopathies (EEs) are a devastating group of severe childhood onset epilepsies with medication resistant seizures and poor developmental outcomes. EEs have strong genetic contributions and are associated primarily with *de novo* mutations in many genes, including $GABA_A$ receptor subunit genes (*GABRs*). Recently, we performed next generation sequencing on patients with a range of EE phenotypes and identified six novel *de novo GABRG2* mutations (A106T, I107T, P282S, R323Q, R323W and F343L). To gain insight into the molecular basis for how these mutations contribute to EEs, we explored and compared the effects of the mutations on the properties of recombinant α1β2γ2L $GABA_A$ receptors transiently expressed in HEK293T cells. Using a combination of flow cytometry, immunoblotting, confocal imaging and patch clamp recording, we found that these *GABRG2* mutations impaired $GABA_A$ receptor biogenesis and/or channel function to different extents. Compared with wild-type α1β2γ2L receptors, $GABA_A$ receptors containing different mutant γ2 subunits had reduced cell surface expression with altered subunit stoichiometry or decreased GABA evoked whole-cell current amplitudes but with different levels of reduction. While a causal role of these mutations cannot be directly established from these results, the functional analysis together with the genetic information suggests that these *GABRG2* mutations may at least be genetic risk factors of EE or could be the major contributors to the affected cases. Our study further expands the *GABRG2* phenotypic spectrum and supports growing evidence that defects in GABAergic neurotransmission participate in the pathogenesis of genetic epilepsies including EE.

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Poster

765. Epilepsy Genetics and Seizure Dynamics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 765.03/C42

Topic: C.07. Epilepsy

Support: NIH NS089397

Title: Scn2a-null heterozygosity improves survival and modifies neurocardiac interaction in the Kcna1-null mouse model of SUDEP

Authors: *V. MISHRA[1], N. GAUTIER[1], B. K. KARUMURI[2], R. LIU[2], I. VLACHOS[2], L. D. IASEMIDIS[2], E. GLASSCOCK[1];
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Abstract: Sudden unexpected death in epilepsy (SUDEP) is the leading cause of epilepsy-related mortality, but its genetic etiology is largely unknown and likely complex involving multiple genes. The *Kcna1* gene encodes Kv1.1 potassium channels that act to dampen neuronal excitability whereas the *Scn2a* gene encodes Nav1.2 sodium channels important for action potential conduction. We investigated the ability of subclinical *Scn2a*-null heterozygosity to act as a protective genetic modifier of epilepsy and premature death in the *Kcna1*-null mouse model of SUDEP. We tested the hypothesis that subclinical *Scn2a* heterozygosity reduces SUDEP incidence in *Kcna1*-null mice by suppressing neurocardiac dysfunction associated with the absence of Kv1.1 channels. SUDEP-prone *Kcna1*-null mice exhibited about a 50% increase in lifespan when heterozygous for the *Scn2a*-null allele, that is $Scn2a^{+/-}$, $Kcna1^{-/-}$. In simultaneous video electroencephalography (EEG)- electrocardiography (ECG) recordings, *Scn2a* heterozygosity did not eliminate seizures in $Kcna1^{-/-}$ mice, but seizure burden was partially reduced due to a significant reduction in seizure durations. Analysis of beat-to-beat heart rate variability (HRV) revealed that $Kcna1^{-/-}$ and $Scn2a^{+/-}$, $Kcna1^{-/-}$ mice exhibit similarly high RMSSD (Root Mean Square of the Successive Differences), suggesting the functional interactions between the two mutations do not involve significant alteration of parasympathetic tone. To measure the association of brain and heart activity in more detail, EEG-ECG interaction dynamics were analyzed by dividing EEG-ECG recordings into 10-s segments and estimating the following variables: 1) brain connectivity across channels at traditional EEG bands (coherence C(band)); 2) complexity of EEG and ECG signals (Shannon's Entropy - ENTR); and 3) heart rate variability (the median (M) and Inter Quartile Range (IQR) of the R peak amplitudes and length of RR intervals from QRS complexes in ECG). The degree of association of the extracted EEG-ECG features over the whole record was then evaluated using the phi coefficient. Analysis of EEG-ECG interaction dynamics revealed a significantly higher degree of association between brain and cardiac activity in double mutant mice compared to $Kcna1^{-/-}$ animals for several different measures, suggesting that *Scn2a*-null heterozygosity reduces SUDEP risk by altering neural control of the heart. These findings expand our understanding of the complex genetic interactions underlying SUDEP and identify EEG-ECG association as a potential new biomarker of SUDEP susceptibility.

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Poster

765. Epilepsy Genetics and Seizure Dynamics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 765.04/C43

Topic: C.07. Epilepsy

Support: NHMRC Project Grant

Title: Identification of seizure susceptibility loci using the Collaborative Cross

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Abstract: AIM: The Collaborative Cross (CC) was originally designed to facilitate rapid mapping of genes in mice using hundreds of recombinant inbred strains derived from eight diverse inbred founder strains. Seizure disorders are complex trait and have been studied for many years, however only a few strongly penetrant candidate genes have been discovered. Recently, identification of mutations on multiple backgrounds has revealed the impact of some lesser penetrant or modifier genes that impact on epileptic seizure severity, latency and form. METHOD: We induced epileptic seizures by intra-peritoneal injection of pentylenetetrazol (PTZ) into 6 to 8 week old CC mice and 4 of the initial founder strains. After injection, each mouse was monitored for 10 minutes. Between 8 to 10 male mice were used for each. Seizure severity was scored using a modified seizure scale (0 – no visible effect; 1 – freezing or immobility; 2 – isolated limb clonus; 3 – generalised clonus; 4 – generalised tonic clonic seizure) and the latency taken to reach each stage was recorded. RESULTS: The CC mice showed highly variable response to PTZ-induced epileptic seizures with some showing high resistance to PTZ challenge whilst others displayed rapid progression to severe seizures. Using QTL analysis, we have identified susceptibility loci and narrowed down target missense mutations for further investigation. CONCLUSION: The CC is a suitable and useful tool for mapping complex traits. Here we have mapped loci for susceptibility to PTZ-induced epileptic seizures in mice. Given the common mechanism of excitotoxicity between seizure disorders, stroke and neurodegenerative disorders such as Alzheimer's disease, we believe the candidates described here may play roles in other neurological conditions where excitotoxicity is implicated.

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Poster

765. Epilepsy Genetics and Seizure Dynamics

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Topic: C.07. Epilepsy

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Title: Microarray based analysis of novel copy number variants of cohort with epileptic patients in Saudi Arabia

Authors: *M. I. NASEER[1], M. FAHEEM[2], A. G. CHAUDHARY[1], F. BIBI[3], M. M. JAN[4], M. RASOOL[1], M. H. AL-QAHTANI[1];
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Abstract: Epilepsy is a neurological condition characterized by recurrent epileptic seizures Epilepsy is a common and disabling neurologic disorder which affects about 1% of the population. Seizures are the result of abnormal electrical activity in the brain and can be profoundly disabling, affecting work, social activity and increasing risk of harm. Specific genetic anomalies or non-genetic factors could lead to epilepsies, but in various cases the underlying cause is unknown. Novel technologies, such as array comparative genomic hybridization (array-CGH), may reveal the copy number variants (CNVs), established as significant risk factor for epilepsies. This study carried out by using high density whole genome Agilent sure print G3 Hmn CGH 2x 400K array-CGH with blood DNA samples from a cohort of forty two epilepic patients to search for novel CNVs associated with epilepsy. We found novel deletion and duplication using microarray data analysis software PARTEK and the novelty of CNVs was checked by using Database of Genomic Variants. Microdeletion of 14q31.1 was observed in four patients including two from the same family with loss of NRXN3 gene; microdeletion of 15q12 with loss of GABRG3 gene, and microduplication of 20q13.33 in three patients with loss of gene group CHRNA4, KCNQ2, EEF1A2 and PPDPF were also found. These CNV findings were confirmed by using real-time quantitative PCR (qPCR). We have described, for the first time, numerous potential CNVs/genes implicated in epilepsy in the Saudi population. The study

presents a better description of the genetic variations in epilepsy, and would eventually enable us to provide a foundation for understanding the critical genome regions which might be involved in the development of epilepsy.

Disclosures: **M.I. Naseer:** A. Employment/Salary (full or part-time):; King Abdulaziz University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; This project was supported by NSTIP strategic technologies program in the Kingdom of Saudi Arabia- Project No. (12-BIO3059-03). The authors also, acknowledge with thanks Science and Technology Unit, Deanship of Scientific Research (DSR), under Grant no. (HiCi/1432/6-1) King Abdulaziz University for their technical and financial support. **M. Faheem:** None. **A.G. Chaudhary:** None. **F. Bibi:** None. **M.M. Jan:** None. **M. Rasool:** None. **M.H. Al-Qahtani:** None.

Poster

765. Epilepsy Genetics and Seizure Dynamics

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Topic: C.07. Epilepsy

Support: 5R01NS086364-02

5R01NS077908-04

Title: Computational models of ictogenesis

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[1]Neurol., Massachusetts Gen. Hospital/Harvard Med. Sch., Charlestown, MA; [2]Kiva Systems, Reading, MA

Abstract: Seizures are so called because we don't know when they will occur, despite many decades of investigation. This situation may have arisen because the relevant parameters are not yet accessible experimentally. To investigate ictogenesis more generally, we created a computational model of the CA3 hippocampal region. The model has a layer of 100 x 100 pyramidal cells, interspersed with a 15 x 15 array of interneurons. We tested two models of spiking neurons - the MacGregor model and the Izhikevich model. Every neuron is connected to a neighborhood of surrounding neurons, using several different strategies for synaptic connectivity. Synapses were designed to undergo activity-dependent short-term depression and

recovery. The initial number of releasable glutamate vesicles in each presynaptic terminal was normally distributed. The amount of glutamate released at a synapse depends on: 1) probability of release of a glutamate vesicle and 2) the number of releasable glutamate vesicles currently available at the synapse. Both spontaneous release and activity dependent release of glutamate are supported by the model. In this work, we are investigating 1) the role that synaptic connectivity strategies play in seizure threshold 2) how the initial distribution of releasable glutamate may play a role in the transition from bursting to ictal like activity. Our initial findings were that a critical level of variance in the availability of releasable glutamate was ictogenic. We are currently completely rebuilding the network in order to replicate this work and ascertain the robustness of our startling initial results.

Disclosures: **T. Jacob:** None. **W. Swiercz:** None. **K. Staley:** None.

Poster

765. Epilepsy Genetics and Seizure Dynamics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 765.07/C46

Topic: C.07. Epilepsy

Support: Epilepsy Foundation Training Grant 330118

NIH NINDS Grant R01 NS072023

NIH NINDS Grant R01 NS062092

CURE Epilepsy

Title: Statistical and computational modeling of meso- and mircoscale human seizure activity

Authors: *G. M. FIDDYMENT[1], O. AHMED[3], L.-E. MARTINET[2], U. EDEN[2], S. CASH[4], M. KRAMER[2];
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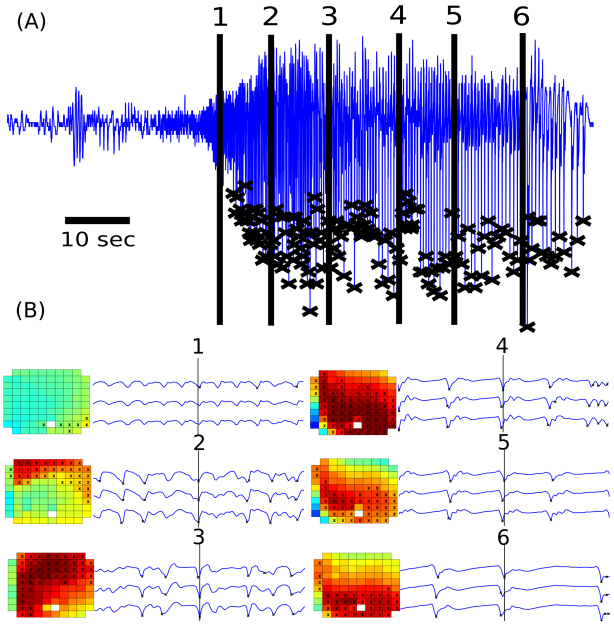
Abstract: Epilepsy is an often debilitating brain disorder, affecting approximately 50 million people worldwide. For a third of these patients, seizures remain poorly controlled despite intensive medical management. To advance the clinical treatment of epilepsy requires a more detailed understanding of the physiology that drives focal initiation and subsequent seizure

spread. Here we describe procedures that link: (I) voltage data from clinical epilepsy patients, (ii) statistical modeling, and (iii) biophysical modeling to advance our understanding of human epilepsy. The data consist of recordings from small patches of cortex using the NeuroPort microelectrode array. These recordings capture both the collective activity of the local field potential (LFP) and the spiking activity of individual neurons. To analyze the data, we build complementary models that characterize how (1) general spatiotemporal features and (2) specific mechanisms contribute to seizure activity. Using descriptive statistics, we show that ictal discharges (IDs) in the LFP comprise two distinct types: large and small amplitude IDs. We then fit statistical models describing the propagation of large and small amplitude IDs across cortex. Models show that large amplitude discharges switch in dominant rhythm from 3-4 Hz to 1-2 Hz and, often, become spatially organized approaching seizure termination. Small amplitude discharges exhibit strong 10 Hz rhythmic activity, but much less spatial organization over the same period. These results suggest that the late stage of seizure is marked by the emergence of different mechanisms, compared to early in the seizure, to support the different dynamics. Additionally, we develop a data assimilation procedure that links observed spike train activity to biophysical parameters. We simulate data from a Hodgkin-Huxley-type model neuron and show that, given only a spike train, the data assimilation procedure accurately recovers hidden model parameters. These methods represent a powerful, data-driven approach to directly investigate the mesoscale dynamics of human seizures.



Disclosures: G.M. Fiddyment: None. **O. Ahmed:** None. **L. Martinet:** None. **U. Eden:** None. **S. Cash:** None. **M. Kramer:** None.

Poster

765. Epilepsy Genetics and Seizure Dynamics

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Topic: C.07. Epilepsy

Support: NIH R01 NS072023

NIH Grant NS062092

Epilepsy Foundation Grant 222178

Title: Neuronal field dynamics interact across spatial scales during propagation of human seizures

Authors: *L.-E. MARTINET[1], G. FIDDYMENT[1], O. J. AHMED[2], E. N. ESKANDAR[3], S. S. CASH[4], M. A. KRAMER[1];
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Abstract: Epilepsy is a complex multiscale disease, extending spatially from microscopic synapses to macroscopic behavioral manifestations. Seizures - the hallmark of epilepsy - exhibit multiscale spatiotemporal dynamics that remain incompletely understood. Here we study the properties of focal seizures using a unique data set of multiscale recordings from microscopic (NeuroPort, 10x10 grid, 0.4 mm spacing) and macroscopic (8x8 grid, 10 mm spacing) subdural electrode arrays implanted in patients with pharmacoresistant epilepsy. We find voltage waves propagating along the brain surface in the local field potential (LFP), as well as in the invasive electroencephalogram (ECoG) recordings. We analyze the spatio-temporal properties of these travelling waves using descriptive statistics including amplitude, speed, orientation and rate within each recording scale. Preliminary results suggest that these statistics change toward the end of the seizure, indicating more spatial and temporal organization of the neural population within scales as well as between scales. Beyond descriptive analysis, we also employ a statistical modeling framework to detail different aspects of the multi-scale dynamics before, during and after seizures: the influence of one channel on itself (self-history dependence), the influence from other channels at the same spatial scale (intrascale relationships), and the influence from channels at other spatial scales (interscale relationships). We hypothesize that the coupling between LFP and ECoG evolves during seizures, with local circuit activity at the microscopic scale being influenced by macroscopic ictal propagation. A deeper understanding of ictal spatio-temporal dynamics within and across scales may have clinical implications, such as the

development of tailored surgical interventions or improved guidance for stimulation induced seizure interruption.

Disclosures: L. Martinet: None. **G. Fiddyment:** None. **O.J. Ahmed:** None. **E.N. Eskandar:** None. **S.S. Cash:** None. **M.A. Kramer:** None.

Poster

765. Epilepsy Genetics and Seizure Dynamics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 765.09/C48

Topic: C.07. Epilepsy

Support: SfN-IBRO International Travel Award

Title: Local hubs of the functional modular structure serve as an indicator of the epileptic zone: an iEEG study

Authors: *B. FILE[1], T. NÁNÁSI[2], B. TÓTH[2], M. MOLNÁR[2], C. J. STAM[3], A. HILLEBRAND[3], I. ULBERT[2], L. ENTZ[4], L. ERőSS[4], D. FABÓ[5];
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Abstract: According to a recent theory, the generation and propagation of the seizure is the consequence of abnormal brain networks, rather than the effect of an isolated pacemaker region. Graph theoretical measurements could be applied on the network of functionally connected brain regions in order to identify the epileptogenic zone (EZ) and examine the neurobiological mechanisms during seizures. The structure of the functional network in the healthy brain can be modelled with a “small-world” topology by a highly modular structure. Previous studies suggested that the epileptic seizures are characterized by a shift toward a more lattice like (ordered) network topology by disconnection of the long range connections. The current study is aimed to investigate the functional modular changes linked to epilepsy. 6 epilepsy surgery patients interictal and ictal intracranial EEG (iEEG) recordings were analyzed. EZs were determined by expert clinicians. After the intervention 5 of the 6 patients were rendered seizure free. Functional brain networks were investigated based on the measurement of phase synchronization (phase lag index; PLI) in gamma (30-45 Hz) frequency band. The functional

networks were partitioned into spatially nonoverlapping groups of nodes. The functional role of each node is characterized by the level of “within- module” connectivity and “between- module” connectivity. Local ”hubs” corresponded to the nodes with a high level of “within- module” and a low level of “between- module” connectivity. The neuronal network changed during seizure activity accompanied by the loss of long range connections and the extensive development of local synchronization. During seizures, the neuronal network moved in the direction of a more ordered, configuration compared to the interictal “small-world” like network organization. Analysing the interictal modular topology resulted that the most prominent local hubs tended to colocalize with the EZ identified by clinicians in the good outcome patients, and located outside of the EZ in the bad outcome patient. In line with previous results we demonstrated that ictal functional networks have a more ordered configuration than interictal ones. In this study we localized the EZ with the local ”hubness” as the topological indicator of the disconnection of long-range connections and strengthening of local connections. The high level of local ”hubness” has a promising clinical relevance as a marker of the EZ even in interictal recordings. The results support and supplement the growing number of evidence, that functional network analysis could be an efficient clinical tool for EZ localization.

Disclosures: **B. File:** None. **T. Nánási:** None. **B. Tóth:** None. **M. Molnár:** None. **C.J. Stam:** None. **A. Hillebrand:** None. **I. Ulbert:** None. **L. Entz:** None. **L. Erőss:** None. **D. Fabó:** None.

Poster

765. Epilepsy Genetics and Seizure Dynamics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 765.10/C49

Topic: C.07. Epilepsy

Support: NIH Grant k08NS069783

Title: Expanding the taxonomy of seizure dynamics

Authors: J. SCOTT[1], Y. BHAGAT[2], C. BERNARD[3], V. JIRSA[3], *W. C. STACEY[2]; [1]Biomed. Engin., [2]Neurol., Univ. of Michigan, Ann Arbor, MI; [3]Aix Marseille Univ., Marseille, France

Abstract: Recent work has shown that focal seizures exhibit a set of general conserved dynamics. We recently developed a mathematical model of seizure dynamics based upon the features of seizure onset and termination[1]. This model was based upon identifying the various types of global behavioral shifts, or bifurcations, that occur going into and out of seizures. In that

initial work, a combination of theoretical and experimental data found that most seizures displayed behavior typical of a specific pair of bifurcations. These two bifurcations impose certain constraints on the seizure dynamics, such as predicting a shift in DC offset at seizure onset and a logarithmic scaling of spike rates near seizure termination. These findings were validated experimentally across brain regions, syndromes, and even across species (humans, mice, rats, zebrafish, etc), suggesting that seizures with vastly different pathophysiologies share fundamental and conserved dynamics. The study also found, however, that in different human patients a small number of recorded seizures (< 20%) displayed behavior suggestive of other types of bifurcations. In this study, we analyzed more than 150 seizures across more than 75 patients to identify the types and prevalence of other types of seizure dynamics at seizure offset. We employ curve-fitting techniques to these data and demonstrate several additional seizure offset behaviors - exponential increase of firing rates (power law scaling), linear change of firing rates (linear scaling), and disorganized firing rates - all of which occur less frequently than the logarithmic scaling described above. Preliminary modeling also shows these different behavioral shifts to be well-represented by bifurcations not described in our original work. These data will be instrumental in developing an expanded taxonomy of seizure dynamics, aiding in the further characterization and prediction of behaviors of various seizure types. [1] Jirsa, V. K., Stacey, W. C., Quilichini, P. P., Ivanov, A. I., & Bernard, C. (2014). On the nature of seizure dynamics. Brain, 137, pp. 2210-2230.

Disclosures: J. Scott: None. **Y. Bhagat:** None. **C. Bernard:** None. **V. Jirsa:** None. **W.C. Stacey:** None.

Poster

765. Epilepsy Genetics and Seizure Dynamics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 765.11/C50

Topic: C.07. Epilepsy

Support: NIH grant NS084142-01

Title: Ictal discharges arise from the ictal wavefront in spontaneous human seizures

Authors: *E. H. SMITH[1], J.-Y. LIOU[2], T. DAVIS[3], E. MERRICKS[4], B. GREGER[5], P. HOUSE[3], G. MCKHANN[2], R. R. GOODMAN[6], R. EMERSON[7], L. BATEMAN[2], A. TREVELYAN[4], C. SCHEVON[2];
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Univ., Newcastle upon Tyne, United Kingdom; [5]Arizona State Univ., Tempe, AZ; [6]Icahn Sch. of Med. at Mount Sinai, New York, NY; [7]Weill Cornell Med. Col., New York, NY

Abstract: The vast majority of seizures terminate naturally, yet almost nothing is known about how this happens, particularly in human epilepsy. We investigate the electrophysiology of spontaneous seizures during the period leading up to seizure termination using microelectrode arrays and electrocorticography in patients undergoing monitoring for surgical treatment of medically refractory epilepsy. We found that, universally, there were steady increases in large-scale synchronization of low-frequency (<50 Hz) local field potentials and in the rate of multiunit firing. Simultaneously there was a gradual decrease in multiunit synchronization in the ictal core, reflected in both microelectrodes and clinical subdural electrodes by significant, progressive decreases in high-gamma power and frequency. We also found evidence that the narrow ictal wavefront initiates discharges of traveling waves into the territory of the seizure core. We present a simple mean field computational model demonstrating that these and related temporal dynamics of human seizure recordings can be explained as a consequence of decreasing excitatory input, as from a more distal or weakening ictal wavefront. Together these results describe an evolving, self-organized structure of human seizures that does not require the often-held assumption of long-range cellular interaction. These results shed new light on our understanding of the structure of human seizure generation, propagation, and termination, and may provide a useful framework to aid in accurate seizure localization for targeted epilepsy therapies.

Disclosures: E.H. Smith: None. **J. Liou:** None. **T. Davis:** None. **E. Merricks:** None. **B. Greger:** None. **P. House:** None. **G. McKhann:** None. **R.R. Goodman:** None. **R. Emerson:** None. **L. Bateman:** None. **A. Trevelyan:** None. **C. Schevon:** None.

Poster

765. Epilepsy Genetics and Seizure Dynamics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 765.12/C51

Topic: C.07. Epilepsy

Title: Cognitive activation can suppress epileptic afterdischarges

Authors: *R. P. LESSER[1], H. J. LESSER[2], P. F. MORRISON[3], W. R. S. WEBBER[1]; [1]Johns Hopkins Hosp, Baltimore, MD; [2]Clin. Trials Unit, Univ. of Pennsylvania, Philadelphia, PA; [3]Neurol., Maine Med. Ctr., Portland, ME

Abstract: We report findings in patients who had subdural electrodes implanted for clinical purposes prior to surgical resections. In these patients we performed cortical stimulation to help localize functional areas prior to the resections. Stimulation at times produced afterdischarges (AD), an unwanted side effect which interferes with the clinical testing and which can result in clinical seizures. (We have previously showed that additional brief pulses of stimulation (BPS) could abort AD, but did so only about half the time; Lesser et al. Neurology 53:2073-2081, 1999). Patients were tested in their hospital rooms, in the Epilepsy Monitoring Unit at John Hopkins. They were awake and comfortable, lying in bed with the head of the bed elevated. We recorded electrocorticographic activity (EcoG) continually. When BPS did not terminate AD, we presented patients with cognitive tasks (subtraction from 2 digit number, spelling word backwards). We found that, although BPS had been unsuccessful, AD could be aborted by the cognitive tasks used on some but not all trials. The tasks were perceived by the patients to be effortful: alertness or attention alone was insufficient to abort AD. Cognitive effort can abort AD occurring throughout the brain regions tested, regardless of whether the regions are thought important for carrying out these cognitive tasks. The cognitive tasks most likely activate a widespread brain network needed to solve the presented problems, with this network not limited to the region with AD. The interaction of this spatially widespread network with the more localized network with AD determines whether AD would be aborted.

Disclosures: **R.P. Lesser:** None. **H.J. Lesser:** None. **P.F. Morrison:** None. **W.R.S. Webber:** None.

Poster

765. Epilepsy Genetics and Seizure Dynamics

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Topic: C.07. Epilepsy

Support: Army Research Laboratory through contract no. W911NF-10-2-0022

John D. and Catherine T. MacArthur Foundation

Alfred P. Sloan Foundation

Title: Brain state predicts success or failure of cognitive effort in suppressing epileptic after discharges

Authors: *S. E. MULDOON[1,2], J. COSTANTINI[1], R. P. LESSER[3], W. R. S. WEBBER[3], D. S. BASSETT[1];
[1]Dept. of Bioengineering, Univ. of Pennsylvania, Philadelphia, PA; [2]US Army Res. Lab., Aberdeen Proving Ground, MD; [3]Johns Hopkins Med. Institutions, Baltimore, MD

Abstract: Cognitive activation can play a role in shifting brain states, but little is known about its effects on pathological brain dynamics in disorders such as epilepsy. Here, we study the role of cognitive activation in suppressing after discharges (AD) in epileptic patients. Electrocorticographic (ECoG) recordings were obtained from patients who had subdural electrodes implanted for localization purposes as a part of efforts to treat their medically intractable epilepsy with surgical resections. During this evaluation, electrical stimulation was performed to help localize motor, sensory, language, and other functional areas. An unwanted effect of stimulation can be the occurrence of afterdischarges (AD), electrical patterns that closely resemble epileptic seizures. In some cases we noted that AD were suppressed by cognitive tasks such as answering a simple math question. We therefore ask how the cognitive effort alters the functional structure of the brain, and whether the initial brain state predicts the success or failure of the cognitive effort in stopping and/or modifying the AD. We quantify brain states using measures of functional network structure derived from ECoG recordings obtained before and after math questions were asked. We observe that answering the math question induces frequency dependent changes in the functional structure that vary depending on whether or not AD terminated. Additionally, we observe that the spatial properties of the community structure present in the initial brain state are correlated with the success of cognitive effort to stop AD. These results indicate that an individual's brain state may tune the success of therapeutic interventions to mitigate epileptiform activity.

Disclosures: S.E. Muldoon: None. **J. Costantini:** None. **R.P. Lesser:** None. **W.R.S. Webber:** None. **D.S. Bassett:** None.

Poster

765. Epilepsy Genetics and Seizure Dynamics

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 765.14/C53

Topic: C.07. Epilepsy

Support: ASU Startup Funds

Title: Phase analysis of network dynamics in human electrocorticography: a potential adjunct to visual inspection for seizure detection

Authors: *K. J. O'NEILL, III[1], K. ASHMONT[1], P. ADELSON[1,2], B. GREGER[1];
[1]Sch. of Biol. Hlth. Sci. and Engin., Arizona State Univ., Tempe, AZ; [2]Barrow Neurolog. Inst. at Phoenix Children's Hosp., Phoenix, AZ

Abstract: One in 26 individuals in the United States will be diagnosed with a seizure disorder at some point in their lives. Of these, 22.5% will be medically intractable, and may seek surgical intervention for palliation or cure. If there is a lack of lateralization or localization, electrocorticography (ECoG) has been used to define the seizure focus. Following focal resection, 50-70% of patients remain seizure free at one year. The current gold standard for seizure focus localization is visual inspection of video and ECoG recordings by an epileptologist. This is a time consuming and subjective process. Quantitative analyses could help reduce the time associated with the review process and introduce objective measures of the complex and dynamic neural processes associated with seizure related electrographic events. We hypothesize that analysis of the phase relationships across ECoG electrodes could serve as a useful adjunct to visual inspection. Given a signal x(t) and its Hilbert transform x'(t), the instantaneous phase $\phi(t)$ of the signal may be calculated by: $\phi(t)=\arctan(x'(t)/x(t))$. Two signals are phase-locked if their instantaneous phase difference $\Delta\phi(t)=\phi1(t)-\phi2(t)$ is concentrated around a specific value ϕlock. The phase lag index (PLI) is a measure of coupling between two electrodes that are separated in space. The PLI is calculated from differences in the instantaneous phase of each signal (Stam, et al. 2007). An asymmetry in the distribution of instantaneous phase difference between two signals requires that one signal consistently lags in time behind the other. PLI is calculated as: $PLI=|\langle sign(\Delta\phi(t))\rangle|$. When PLI=1, the signals are perfectly phase locked at $\phi lock=\langle\Delta\phi(t)\rangle$. When PLI=0, the signals are non-coupled. PLI can be used to characterize the nature of the phase relationship between two signals, and evaluate functional connectivity and network dynamics. Following analysis of the ECoG data from 3 patients containing 12 seizures, we observed that the average PLI values fluctuate about a baseline value during non-ictal periods, but displayed a notable increase from the mean during ictal events. For some seizures, there appeared to be a measurable increase in coupling prior within the first few minutes to the clinically determined seizure onset times. These results suggest that PLI could assist in seizure detection by directing epileptologists' attention during inspection of ECoG recordings, and could ultimately lead to improved patient care.

Disclosures: **K.J. O'Neill:** None. **K. Ashmont:** None. **P. Adelson:** None. **B. Greger:** None.

Poster

766. Epilepsy Networks and Channels

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 766.01/C54

Topic: C.07. Epilepsy

Title: Ketogenic diet induces changes in purine-dopamine neuronal system interactions

Authors: J. G. RUBIN, M. L. DYER, *W. H. CHURCH;
Chemistry/Neuroscience Program, Trinity Col., Hartford, CT

Abstract: Previous research from this lab has indicated that a three-week ketogenic diet (KD) increases dopaminergic activity in the motor and somatosensory cortex areas of adult mice. Adenosine has been implicated in the therapeutic effect of the KD and the purine system is known to modulate dopaminergic activity. This study evaluated whether the changes seen in dopaminergic activity were associated with changes in purine neurochemistry. Samples from the previous study were analyzed using a high performance liquid chromatography (HPLC) method for the quantification of adenosine, hypoxanthine, xanthine, and inosine. No alteration in tissue levels of these purinergic compounds was found in the KD treatment group when compared to the control diet group. Cortical adenosine tissue levels and ß-hydroxybutyrate (BHB) blood levels were negatively correlated in the KD treatment group but not in the control diet group. A negative correlation was also observed between the adenosine metabolites (xanthine, hypoxantine and inosine) and BHB blood levels in the KD treatment group. Cortical dopaminergic activity (as measured by the DOPAC+HVA/DA ratio) and adenosine tissue levels were negatively correlated in the control diet group ($r=-0.70$, $p=0.054$). No such correlation was found in the the KD treatment group. These findings support previous literature regarding interaction between the dopaminergic and purinergic neuronal systems and suggest a possible ketogenic diet-induced change in the purinergic modulation of cortical dopaminergic activity in mice.

Disclosures: J.G. Rubin: None. **M.L. Dyer:** None. **W.H. Church:** None.

Poster

766. Epilepsy Networks and Channels

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Topic: C.07. Epilepsy

Support: Dr. Ralph and Marian Falk Medical Research Trust

Title: Functional synaptic connectivity during development of hippocampal neuronal networks *in vitro*

Authors: *J. SURESH[1], A. BHANSALI[2], J. MARKS[3], J. WANG[4], A. K. TRYBA[4], W. VAN DRONGELEN[4];
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Abstract: Dissociated rat hippocampal cell cultures develop unique network activity patterns at different maturation stages in-vitro. An important component of this network behavior is determined by synaptogenesis. In a previous study, we quantified anatomical synaptogenesis by counting synapses at four critical stages of maturation - 5, 8, 14 and 20 days *in vitro* (DIV). We are now interested in determining the development of functional synaptic connectivity at these stages. To accomplish this, we made whole cell patch clamp recordings of pairs of connected neurons to determine the strength of synaptic connectivity. We computed spike-triggered averages (STA) of postsynaptic activity triggered by action potentials in the presynaptic neuron. We compared the area under the curve (AUC) for STAs during spontaneous and evoked synaptic activity to quantify synaptic connectivity at different maturation stages. Evoked activity was achieved by current injections leading to bursts in the presynaptic neuron. Preliminary results show that at 5 DIV, there is no spontaneous spiking as evidenced by sub-threshold membrane potential values. However current injections in the presynaptic neuron were able to trigger spikes in the postsynaptic neuron. By 8 DIV, there is significant amount of spontaneous spiking activity and the AUC of STA during evoked activity is larger compared to that at 5 DIV. However comparison of AUC during spontaneous and evoked activity within this stage shows no clear differences. At 14 DIV, in addition to spiking and bursting activity, there are also periods of sustained depolarization, characteristic of paroxysmal depolarization shifts (PDS). There is a clear increase in the AUC during spontaneous and evoked activity compared to 8DIV. Moreover, there is a relative increase in AUC for evoked activity when compared to spontaneous activity at this maturation stage. At 20 DIV, there is a further increase in the AUC of STAs during spontaneous and evoked activity compared to 14 DIV. The relationship between these findings and emergent network activity patterns, as well as histology of maturing in-vitro cell cultures will be discussed.

Disclosures: J. Suresh: None. **A. Bhansali:** None. **J. Marks:** None. **J. Wang:** None. **A.K. Tryba:** None. **W. van Drongelen:** None.

Poster

766. Epilepsy Networks and Channels

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 766.03/C56

Topic: C.07. Epilepsy

Title: Protective effect of erythropoietin, but not that of Epotris, on cognitive function is compromised in rats subjected to status epilepticus when raised in enriched environment

Authors: *L. BEZIN[1,3], M. OGIER[2,3], J. BODENNEC[1,3], S. PANKRATOVA[4], V. BEREZIN[4], A. BELMEGUENAI[1,3];
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Abstract: Cognitive impairment is a condition frequently associated with pediatric epilepsy that can severely affect the quality of life of children with epilepsy and their family. Therefore, there is an urge to find therapeutical and alternative interventions aimed at preventing or reducing the decline of cognitive functions. In rats raised in conventional environment (CE), we showed that recombinant erythropoietin (Epo) treatment (5,000 IU/kg daily for 5 consecutive days) following pilocarpine-induced status epilepticus (SE) at weaning prevented alteration of spatial memory and synaptic plasticity. Housing rats in an environmental enrichment (EE) alone just after SE produced the same effects as Epo alone. However, the amplitude of LTP in rats subjected to SE and raised in EE did not reach the magnitude measured in healthy rats raised in EE. We therefore tested the hypothesis that the combination of Epo and EE after SE may help to reach this goal. Unexpectedly, we observed that this combination totally abolished the beneficial effects of either Epo or EE alone in rats subjected to SE. We then tested whether this detrimental combination could be avoided by using Epotris, a non-erythropoietic derivative of Epo. We showed that Epotris exerted neuroprotective effects on LTP and spatial learning after SE in rats raised in CE, and that these effects were not compromised when rats were raised in EE. However, Epotris in combination with EE was not able to restore the amplitude of LTP measured in healthy rats raised in EE. Our results thus showed that the protective effects of Epotris are independent of the quality of the living environment, and suggest that non-erythropoietic derivatives of Epo may be preferred over recombinant or native Epo to protect learning and memory following severe brain injury such as occurs after SE.

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Poster

766. Epilepsy Networks and Channels

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The Japan Epilepsy Research Foundation

The Mother and Child Health Foundation

NPO Rett Syndrome Support Organization

Title: Functional analyses of the CDKL5, a causative gene for severe neurodevelopmental disorders accompanied by intractable epilepsies

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Abstract: The Cyclin-dependent kinase-like 5 (CDKL5) gene encodes for a serine-threonine kinase sharing homology to Mitogen-activated kinases (MAPKs) and Cyclin-dependent kinases (CDKs). Recently, mutations in the CDKL5 gene have been identified in the patients with severe neurodevelopmental disorders accompanied by intractable epilepsies, i.e. West syndrome or atypical Rett syndrome, suggesting its critical role in neurodevelopment. However, the molecular functions or pathomechanisms caused by its mutations are largely unknown. Aiming to solve these problems, we have taken multidimensional strategies, combining an unbiased interactome approach and a targeted loss-of-function (LOF) approach. For the interactome approach, we

performed the yeast two-hybrid screening and identified several CDKL5 interacting proteins. For the LOF approach, we have generated the Cdkl5 knockout mouse and analyzed the neurological phenotypes. The combination of these approaches suggested us possible mechanisms of CDKL5 regulating neural functions during development.

Disclosures: **T. Tanaka:** None. **K. Okuda:** None. **S. Kobayashi:** None. **T. Murakami:** None. **M. Fukaya:** None. **K. Takao:** None. **A. Watanabe:** None. **M. Hagiwara:** None. **M. Mizuguchi:** None. **H. Sakagami:** None. **T. Miyakawa:** None. **T. Manabe:** None.

Poster

766. Epilepsy Networks and Channels

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 766.05/C58

Topic: C.07. Epilepsy

Title: Effect of pinealectomy on experimental absence seizures

Authors: *A. DE FUSCO[1], S. MOYANOVA[1], I. SANTOLINI[1], R. CELLI[1], M. MADONNA[2], C. SCHWARZER[3], F. NICOLETTI[1,4], J. TCHEKALAROVA[5], R. T. NGOMBA[1]; [1]Neuropharm., [2]IRCCS INM Neuromed, Pozzilli, Italy; [3]Dept. of Pharmacol., Innsbruck Med. Univ., Innsbruck, Austria; [4]Dept. of Physiol. and Pharmacol., Sapienza Univ., Rome, Italy; [5]Inst. of Neurobiology, Bulgarian Acad. of Sci., Sofia, Bulgaria

Abstract: Melatonin, an endogenous hormone with neurotransmitter properties that regulates the circadian rhythms is mainly produced by the pineal gland. Melatonin has been shown to positively modulate seizures and depressive-like comorbidity in the kainate model of epilepsy (Tchekalarova et al., 2013; Petkova et al., 2014). We investigated the effects of removal of the pineal gland on pentylenetetrazole (PTZ)-induced absence-like seizures. Acute subcutaneous injections of PTZ (21 mg/kg b.w.) resulted in bilateral synchronous spike and wave discharges (SWDs) and associated behavioral arrest, vibrissae twitching and facial myoclonus. Rats were maintained in 12 hours light-12 hours dark conditions. We evaluated the effect of PTZ in pinealectomized- and sham-operated Wistar rats on EEG during dark and light phases. We took into consideration the biological peak of melatonin secretion and we injected PTZ four hours after beginning of the dark phase. Another group of Wistar rats was treated with PTZ at matched time points during the light phase. EEG analysis showed that pinealectomized rats have increased susceptibility to PTZ-induced absence seizures with about two-fold greater number of SWDs compared to sham-operated rats, both in dark and light phases. The results demonstrate that modification of the melatoninergic system influences the brain thalamo-cortical network,

which is responsible for the development of absence epilepsy, and suggest a protective role of the endogenous melatonin against PTZ-induced absence-like seizures. Tchekalarova et al., Epilepsy Behav. 2013 Apr;27(1):174-87. Petkova et al., Epilepsy Behav. 2014 Feb;31:198-208.

Disclosures: **A. De Fusco:** None. **S. Moyanova:** None. **I. Santolini:** None. **R. Celli:** None. **M. Madonna:** None. **C. Schwarzer:** None. **F. Nicoletti:** None. **J. Tchekalarova:** None. **R.T. Ngomba:** None.

Poster

766. Epilepsy Networks and Channels

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 766.06/C59

Topic: C.07. Epilepsy

Support: BBSRC studentship

Title: Modulation of intracellular ATP influences seizure activity via the activity-dependent release of adenosine

Authors: ***J. HALL**, B. G. FRENGUELLI;
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Abstract: The purine nucleoside adenosine is involved in the regulation of both normal physiological processes, such as the modulation of neuronal excitability, and in the pathophysiology of neurological conditions such as epilepsy. Adenosine, via its inhibitory A_1 receptor raises the threshold for seizure activity and its release during seizures results in the attenuation and termination of the seizure. Adenosine has thus been described as an endogenous anticonvulsant. However, brain injury causes a rapid decline in cellular ATP levels, which can be long lasting. Given that ATP represents the primary reservoir for adenosine, this has implications for the availability of adenosine after brain injury and the propensity to both seizures in the acute post-injury period, and the initiation of post-traumatic epileptogenesis. We have previously shown that the provision of ribose (1 mM) and adenine (50 μM; "RibAde") in the incubation medium of acutely-prepared hippocampal slices can restore tissue ATP levels to those found *in vivo*[1]. We have also shown that this translates into greater adenosine release in response to physiological and pathological stimuli[1,2]. We have now tested whether RibAde can influence seizure activity, and, as a comparator, used creatine (1 mM), which, via its conversion to phosphocreatine, serves as a buffer against ATP metabolism and reduces adenosine release[2]. Hippocampal slices exposed to nominally Mg^{2+}-free aCSF and 4-AP (50 μM) showed regular

bursts of seizure activity and associated adenosine release, as measured with adenosine biosensors. Three-hour pretreatment of slices with RibAde resulted in greater seizure-induced adenosine release compared to control and creatine slices. In addition, RibAde reduced the frequency of spiking and seizure intensity as well as increased the time between seizures. In contrast, seizure intensity was increased in creatine-treated slices and the time between seizures was reduced compared to RibAde. These studies provide evidence for the value of using RibAde to increase ATP levels in the injured brain. Given the prior safe use of ribose and adenine in humans, RibAde may be a means to improve brain recovery after injury and thus mitigate against the mortality and morbidity associated with such insults. 1) zur Nedden, S., et.al., 2011, J Neurosci, 31, 6221-34. 2) zur Nedden, S., et.al., 2014, J Neurochem 128: 111-24

Disclosures: J. Hall: None. **B.G. Frenguelli:** Other; Bruno G. Frenguelli is a Non-Executive Director of Sarissa Biomedical, the company that manufactures adenosine sensors and from which the sensors were purchased.

Poster

766. Epilepsy Networks and Channels

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 766.07/C60

Topic: C.07. Epilepsy

Support: NIH Grant 5R44NS062477-07

Title: Stimulation-based endpoints for assessing seizurogenic activity with multiwell microelectrode array technology

Authors: *D. C. MILLARD, A. M. NICOLINI, C. A. ARROWOOD, J. D. ROSS;
Axion Biosystems, Atlanta, GA

Abstract: The lack of advancement in anti-epileptic drugs (AEDs) over the last 30 years, along with the continued need for improved proconvulsant screening in drug safety, motivates the need for new assays of seizurogenic neural activity. Previous work has established an *in vitro* approach for detecting and quantifying seizurogenic activity using multiwell microelectrode array (MEA) technology, providing a predictive and high-throughput avenue for the evaluation of the efficacy of AEDs and the proconvulsant risk of other drug candidates. However, incorporation of electrical and optogenetic stimulation to directly evoke neural activity may lead to improved sensitivity for *in vitro* seizurogenic assays. Here, we present an assay of seizurogenic activity based upon the Axion BioSystems Maestro multi-well MEA system. We

used previously published metrics for the detection of burst spiking events and the quantification of synchronization across a neural population, triggered on external stimuli. Data are included from rat cryopreserved cortical neurons, in response to pharmacological manipulation with AEDs (i.e. Carbamazepine, Phenytoin, Tiagabine) and reference compounds with known proconvulsant risk (i.e. 4-Aminopyradine, Strychnine, Pentylenetetrazole, Picrotoxin). Our results support the combined use of evoked and spontaneous neural activity, collected using multi-well MEA technology, for the high throughput evaluation of complex neuronal networks *in vitro* to inform the development of AEDs, while also quantifying the proconvulsant risk of candidate pharmaceuticals in a pre-clinical setting.

Disclosures: D.C. Millard: A. Employment/Salary (full or part-time):; Axion Biosystems, Inc. **A.M. Nicolini:** A. Employment/Salary (full or part-time):; Axion Biosystems, Inc. **C.A. Arrowood:** A. Employment/Salary (full or part-time):; Axion Biosystems, Inc. **J.D. Ross:** A. Employment/Salary (full or part-time):; Axion Biosystems, Inc.

Poster

766. Epilepsy Networks and Channels

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: C.07. Epilepsy

Support: NIH R01 NS081243

NSF GRFP DGE 1326120

NSF IGERT DGE 0903667

Title: Properties of 4-aminopyradine induced epileptiform activity: multichannel electrophysiology and optical coherence tomography *in vitro*

Authors: *T. L. MYERS, O. C. GONZALEZ, M. M. EBERLE, D. BINDER, H. PARK, M. BAZHENOV;
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Abstract: 4-aminopyradine (4AP) blocks the I_A channel, an outward voltage-gated potassium current that may trigger epileptiform activity. While precise mechanisms for seizure initiation are still unknown, 4AP is a well-established model for epilepsy for both *in vitro* and *in vivo* studies. Here, we studied the effects of varying 4AP concentrations on the mouse hippocampus activity *in vitro* using simultaneous multi-electrode array (MEA) recordings and optical coherence

tomography (OCT). We observed distinct synchronous firing patterns following bath application of 4AP. Lower concentration (25 – 75 uM) generated continuous synchronous epileptiform activity at lower frequencies (0.1 – 0.2 Hz) and amplitudes (0.3 – 0.4 mV). Bath applications of 100 – 200 uM 4AP led to the development of higher amplitude (0.5 – 0.6 mV) and frequency (0.3 – 0.5 Hz) burst-firing of the hippocampal network. Spatiotemporal analysis revealed that increases in 4AP concentration elicited more focal epileptiform activity as compared to more diffuse activity at lower concentrations. *In vivo* studies found that 4AP induced seizure in mouse cortex can be optically detected using OCT. However, it remained unclear to what extent the changes of the optical signal depend on the increased blood flow through the tissue during seizure. Here, we found decreases in the OCT measured attenuation coefficient, which temporally aligned with the onset of the 4AP induced epileptiform activity in the hippocampus. Overall, we show distinct spatiotemporal dynamics for 4AP induced activity in a concentration dependent manner, and revealed that these forms of neuronal activity can be optically detected *in vitro.* This refutes the hypothesis that the entirety of the optical signal detected *in vivo* 4AP induced seizures are due to changes in blood flow, and that there is a component that may reveal changes in cell swelling associated with intense electrical activity during seizure.

Disclosures: T.L. Myers: None. **O.C. Gonzalez:** None. **M.M. Eberle:** None. **D. Binder:** None. **H. Park:** None. **M. Bazhenov:** None.

Poster

766. Epilepsy Networks and Channels

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 766.09/C62

Topic: C.07. Epilepsy

Support: SNF grant 323530_158125

SPUM ME9294

Title: Propagating spikes are associated with the emergence of neocortical high-frequency oscillations remote from the epileptic focus in the mouse-model of temporal lobe epilepsy

Authors: *L. SHEYBANI[1,2], F. PITTAU[3], G. BIROT[3], S. VULLIEMOZ[3], M. SEECK[3], K. L. SCHALLER[4], C. M. MICHEL[2], C. QUAIRIAUX[2];
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Geneva, Switzerland; [4]Clin. Neuroscience, Univ. Hosp. of Geneva, Neurosurg. Clin., Geneva, Switzerland

Abstract: In focal epilepsies, the epileptic focus may affect the activity of remote brain regions leading to the progressive development of an epileptic network. Fast ripples (FRs, 200-550 Hz), a subpopulation of high-frequency oscillations (HFOs, 80-550 Hz), are believed to be a marker of epileptogenic brain areas and have been used in humans and animal models of epilepsy to locate epileptic foci. We hypothesize that FRs could hence be used to locate normal brain regions progressively recruited within the epileptic network. We studied the expression of FRs outside of the initial epileptic focus in the kainate mouse-model of hippocampal sclerosis. In a first step, a total of 23 adult mice were recorded with 32 surface electrodes prior (internal controls) to injection of kainate in the left hippocampus (LH), then at day 7, 14 and 28 after injection. Surface recordings allowed us to map the epileptic network and to identify brain regions expressing FRs using a newly developed automated detector of FRs. The epileptic network was characterized by propagating spikes (PrS) starting from the hippocampus and propagating to all contacts in < 20 msec. Their occurrence increased throughout the disease. While prior to kainate injection physiological FRs could be observed mainly over the barrel fields, they then appeared massively over the LH over time and also progressively over the right hippocampus and neocortical frontal areas. Those FRs recorded after injection had properties different than the physiological FRs, i.e. longer duration and lower intrinsic frequency. Importantly, outside of the LH, neocortical FRs were tightly coupled with the occurrence of PrS: the further away from the LH FRs were recorded, the higher their chance to be associated with PrS. Furthermore, the presence of a FR during a PrS was associated with a higher amplitude of the PrS; if the FR occurs over frontal areas, its amplitude was even higher. This was then confirmed using intracerebral recordings. 9 of these mice were recorded with 4 x 16 electrodes in the left motor and cingulate cortices and both hippocampi revealing that the onset of frontal FRs appeared during a preferential phase of the local-field potential, within the frequency band of PrS. In conclusion, we show for the first time that in addition to the generally accepted notion that pathological FRs are strictly found in the seizure-onset zone, neocortical FRs can occur in non-injured neocortical areas and can be triggered by epileptic spikes. This is of utmost importance, as FRs are dysfunctional activities ordinarily seen in epileptogenic tissues.

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Poster

766. Epilepsy Networks and Channels

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 766.10/C63

Topic: C.07. Epilepsy

Title: Modulation of EEG by hyperventilation in an animal model of absence seizures

Authors: *K. A. SALVATI, N. N. KUMAR, M. P. BEENHAKKER;
Dept. of Pharmacol., Univ. of Virginia, Charlottesville, VA

Abstract: Absence epilepsy is a non-convulsive generalized seizure disorder characterized by a sudden arrest of consciousness and 3-5Hz spike-and-wave discharges (SWDs) in electroencephalography (EEG) recordings (Crunelli and Leresche, 2002). Absence seizure generation involves reciprocal circuitry between neurons of the thalamus and cortex. Voluntary hyperventilation reliably triggers SWDs in the EEG of absence patients and, therefore, is used to clinically diagnose this childhood form of epilepsy (Penry and Dreifuss, 1969; Adams and Leuders, 1981). The mechanism(s) fully elucidating how induced-hyperventilation precipitates SWDs remains unknown, despite the knowledge of such a link for over four decades (North et al., 1990; Wirrell et al., 1981). Many studies demonstrate that hyperventilation and the associated change in brain pH modulate neuronal excitability (Dulla et al., 2005) and epileptic activity (Miley, and Forster, 1977). Neurons sensitive to brain pH are known as central respiratory chemoreceptors (Guyenet et al., 2010). Collectively, these neurons modulate their activity through pH-sensitive ion channels and G-protein coupled receptors (GPCRs) (Guyenet et al., 2010). Two GPCRs, OGR1 and GPR4, are proposed to mediate neuronal activity in the brain (Schneider et al., 2012; Huang et al., 2007). We set out to determine whether hyperventilation alters SWDs in the EEG of two rodent models of absence epilepsy: the DBA/2J mouse and the WAG/Rij rat. To do so, we pharmacologically induced hyperventilation *in vivo* (Cotten, 2013) and measured ensuing SWD activity. Preliminary data from these experiments indicates that SWD frequency and duration increases following i.p. injection in both our rodent models compared to vehicle injection. Our preliminary EEG studies motivated our hypothesis that pH-sensitive neurons in the thalamus trigger hyperventilation-induced SWDs. To begin testing this hypothesis, we first set out to characterize the level of expression of OGR1 and GPR4 in the thalamus. We used multi-label fluorescence *in situ* hybridization to assess expression. Our data shows that GPR4, but not OGR1, mRNA is abundant in the thalamus. Moreover, GPR4 mRNA is localized to excitatory ($VGLUT2^{+}$) cells within the thalamus. Our future experiments will assess how these putative pH-sensitive neurons are modulated by hyperventilation-induced changes in brain pH.

Disclosures: K.A. Salvati: None. **N.N. Kumar:** None. **M.P. Beenhakker:** None.

Poster

766. Epilepsy Networks and Channels

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 766.11/C64

Topic: C.07. Epilepsy

Title: Manipulating the medial entorhinal cortex via dreadd receptors in a mouse model of temporal lobe epilepsy

Authors: *B. S. BARKER, J. A. HOUNSHELL, R. P. GAYKEMA, M. K. PATEL;
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Abstract: Manipulating the Medial Entorhinal Cortex via DREADD Receptors in a Mouse Model of Temporal Lobe Epilepsy Temporal lobe epilepsy (TLE) is the most common form of adult epilepsy involving the limbic structures of the temporal lobe. In TLE, surviving medial entorhinal cortex (mEC) neurons become intrinsically hyper excitable, leading to excessive excitatory input into the hippocampus. Increased mEC-hippocampal innervation is believed to play a significant role in the initiation and propagation of seizures in TLE. The ability to manipulate specific regions of the brain via activation of excitatory (G_q) or inhibitory (G_i) designer receptors exclusively activated by a designer drugs (DREADD) using Clozapine N-Oxide (CNO) is a powerful tool that enables us to selectively study the role of the mEC in TLE. In the kindling model of epilepsy, motor seizures are induced via an electrical stimulation of the hippocampus at a pre-determined intensity known as an after discharge threshold (ADT). In mice expressing the G_i DREADD receptor, inactivating the mEC with 5 mg/kg CNO resulted in a dramatic increase in the ADT compared to control mice. To further test the role of the mEC in TLE, we examined the effects of activating the mEC in spontaneous seizing mice produced by the continuous hippocampal stimulation (CHS) protocol. Activating the mEC in CHS mice expressing the G_q receptor with CNO (3 mg/kg) produced an increase in seizure frequency compared to animals given saline. Activation of the mEC in control, non-epileptic mice expressing the G_q receptor with CNO (3 mg/kg) had no effect. This study validates the crucial role of the mEC in initiation and propagation of seizures in temporal lobe epilepsy.

Disclosures: **B.S. Barker:** None. **J.A. Hounshell:** None. **R.P. Gaykema:** None. **M.K. Patel:** None.

Poster

766. Epilepsy Networks and Channels

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 766.12/C65

Topic: C.07. Epilepsy

Support: Citizens United for Research in Epilepsy (CURE)

Epilepsy Foundation

Title: Changes in functional imaging of DBA/1 mouse brain in seizure-induced respiratory arrest

Authors: *S. KOMMAJOSYULA[1], M. E. RANDALL[2], T. J. BROZOSKI[3], B. ODINTSOV[4], C. L. FAINGOLD[2];
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[4]Biomed. Imaging Center, Beckman Inst., Univ. of Illinois, Urbana-Champaign, IL

Abstract: Introduction: Sudden unexpected death in epilepsy (SUDEP) accounts for 8-17% of total epileptic deaths. Generalized seizures and respiratory dysfunction are major proposed mechanisms of human SUDEP. DBA/1 mice are a SUDEP model that is susceptible to generalized audiogenic seizures (AGSz), resulting in seizure-induced respiratory arrest (S-IRA). Magnetic resonance imaging (MRI) studies of SUDEP patients observed atrophy in specific brainstem structures, implicating them in the neuronal network for SUDEP (Mueller et al., Neuroimage Clin 2014; 5: 208-16). Therefore, we evaluated changes in brain activity using manganese-enhanced MRI (MEMRI) to map the neuronal network of DBA/1 mice and compare it with the human network. Methods: Manganese chloride (80 mg/kg) was injected SC 10 hr prior to AGSz induction in 3 groups of DBA/1 mice: (1) mice that exhibited AGSz with S-IRA; (2) mice that exhibited AGSz without S-IRA [NS-IRA, induced with 45 mg/kg (i.p.) fluoxetine]; and (3) mice that were not exposed to sound or AGSz (controls). Immediately after AGSz, the mice were anesthetized and their brains fixed. The fixed brains were scanned *in situ* with a 14.1T Varian microimagerc consisting of a vertical bore magnet (89mm) and a 600 MHz Varian Unity/Inova NMR spectrometer. A high image quality spin-echo-multi-slice protocol was employed for the T1 mapping. TIFF images were analyzed using Image J (ver. 1.49h), and a mixed-factor ANOVA (SPSS ver22). Results: The MEMRI data indicate a significant ($p<0.001$) overall increase in the neuronal activity of the NS-IRA group vs S-IRA and control DBA/1 group 110.24±0.72 vs 104.34±0.70 and 103.26±0.61. Detailed analysis revealed significant ($p<0.05$) increases in activity at Kölliker-Fuse nuc. (123.6±4.4 vs 103.4±1.7), pontine raphe nuc. (126.1±6 vs 104.2±1.8), and inferior colliculus (IC) (111.5±2.7 vs 102.1±0.6) at AP -5.3 (Franklin and Paxinos Mouse Stereotaxic Atlas, 1997); dorsomedial periaqueductal gray (PAG) activity was also significantly elevated (113.6±1.6 vs 100.7±1.7) at AP -3.4, in the NS-IRA compared to S-IRA group, suggesting action of fluoxetine at these regions in preventing S-IRA. Discussion: These results indicate that the neuronal network for AGSz and S-IRA in DBA/1 mice include several nuclei that have been implicated in other AGSz models. This network also contains structures which exhibited atrophy in neuroimaging studies in human SUDEP, including PAG, IC, and raphe nuclei (Mueller et al., 2014). The similarities of these neuroimaging data to

human MRI studies supports increased relevance of the DBA/1 mouse model to human SUDEP. (Support: Epilepsy Foundation, CURE)

Disclosures: S. Kommajosyula: None. **M.E. Randall:** None. **T.J. Brozoski:** None. **B. Odintsov:** None. **C.L. Faingold:** None.

Poster

766. Epilepsy Networks and Channels

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 766.13/C66

Topic: C.07. Epilepsy

Support: Italian Health Ministry (Ricerca Corrente)

Italian Health Ministry (GR-2011- 02348633)

Title: Seizure-like events in the olfactory cortex of the isolated guinea-pig brain are initiated by extracellular potassium changes

Authors: *L. M. UVA, M. CHIKHLADZE, S. SACCUCCI, M. MORBIN, M. DE CURTIS; Fondazione Inst. Neurologico C. Besta, Milano, Italy

Abstract: The olfactory region has been described as an epileptogenic structure. In a previous paper (Uva et al., 2013) we showed that arterial application of the potassium channel blocker 4-aminopyridine (4AP; 50μM) in the isolated guinea-pig brain maintained *in vitro* induces different and independent seizure patterns in the olfactory and limbic regions. Field potentials (FPs) recordings in piriform cortex (PC) at 3-400μm in depth showed that epileptiform activity starts with runs of fast activity around 30Hz, followed by a rapid positive component (phase 1), a second negative component with fast activity superimposed (up to 60Hz) and 10hz activity (phase 2) before the transition to spikes (phase 3). Simultaneous extra and intracellular recordings demonstrated that seizures-like events (SLEs) correlate with depolarization of superficial layer neurons of the PC, whereas deep layers neurons are poorly involved. The aim of this study is the investigation of the mechanisms underlying the SLE onset. We arterially applied 4AP to the isolated guinea-pig brain maintained *in vitro* and recorded SLE activity with glass pipettes inserted at the surface of the cortex and at 3-400μm in depth, or with a 16-channel linear silicon probes (50 contact separation) to monitor the change of FPs components in depth. We observed a large and slow negative potential in the most superficial positions at SLE onset suggesting ionic shifts. We then monitored K^+ changes simultaneously in two or three different

depth positions in PC (from surface to 750µm in depth) with ion-sensitive electrodes. Data showed that SLE onset correlates with a rapid increase of K^+ at the surface of the PC (K^+ peak during phase 2 of SLE) and slower increase in deeper layers (K^+ peak during phase 3 of SLE). Experiments performed in guinea-pig PC-slices cut parallel to the surface (500µm thick) and including only the most superficial portion of the cortex confirmed the ability of superficial layer to generate K^+ increases. This K^+ shift could explain 1) the neuronal firing abolishment in layer II during phase 2 that gradually restored before seizure end (Uva et al., 2013), 2) the abolishment of the response evoked by lateral olfactory tract (LOT) stimulation during SLE, 3) the scarse involvement of layer III cells. To identify the source of the superficial K^+ shift we looked at morphology of PC Ia layer, containing LOT axons, at the electron microscopy. The absence of myelin observed in layer Ia could facilitate the large release of K^+ from LOT axons during 4AP-induced activity, contributing to K^+ rapid increase at SLE onset. The next step is the study of layer Ia astrocytes, that could decrease their K^+ buffering capability after 4AP application.

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Poster

766. Epilepsy Networks and Channels

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 766.14/C67

Topic: C.07. Epilepsy

Title: Reduced thalamic expression of thrombospondin-1 in a rat model of spontaneous absence epilepsy

Authors: I. SANTOLINI[1], M. GUIDUCCI[2], T. IMBRIGLIO[1], R. CELLI[1], M. CANNELLA[1], M. MOTOLESE[1], V. D'AMORE[1], *R. GRADINI[3,1], G. VAN LUIJTELAAR[4], P. PARISI[5], F. NICOLETTI[1,6], P. STRIANO[7], R. T. NGOMBA[1];
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Abstract: A growing body of evidence suggests a potential role for the α2δ subunit of voltage-gated Ca2+ channels (VGCCs) in the pathophysiology of non convulsive epilepsy. The mutant mouse ducky, which carries a mutation in the gene encoding for the α2δ-2 protein, is characterized by absence seizures and ataxia. In addition, gabapentin and pregabalin, which bind to, and negatively modulate α2δ-1 and α2δ-2 proteins may precipitate absence seizures in humans. α2δ subunit is a key player of both trafficking and current amplitude and kinetics of high-voltage activated (HVA) Ca2+ channels, indeed it has been shown that Ca(v)2.3 channels are critical for oscillatory burst discharges in the thalamic reticular nucleus (nRT) neurons and for the expression of absence epilepsy (Zaman et al., 2011). Although ducky mice show absence epilepsy, there is no evidence of which anatomical area of the thalamo-cortical network ignites the development of absence seizures in these mice. At least α2δ-1 has functions that lie beyond the regulation of VGCCs by functioning as a high affinity receptor for the developmental protein thrombospondins (TSPs). Interaction between TSPs and α2δ-1 appears to be instrumental for the formation of new excitatory synapses in the CNS (Eroglu et al., 2009). This prompted us to study whether changes in the expression of TSPs are associated with absence epilepsy in experimental animal models and humans. We used WAG/Rij rats, which develop spontaneous absence seizures after 2-3 months of age. The transcript of TSP-1 was largely reduced in the ventrobasal thalamus of both pre-symptomatic and symptomatic WAG/Rij rats, as compared to age-matched non-epileptic control rats. This reduction was region-specific because it was not observed in the somatosensory or primary motor cortex of WAG/Rij rats. We speculate that a reduced production of TSP-1 with an ensuing defect in synaptogenesis in the ventrobasal thalamus contributes to the pathophysiology of absence epilepsy at least in WAG/Rij rats. We are currently extending the study to other rodent models of absence epilepsy and we are also searching for polymorphic variants in the gene encoding for TSP-1 and α2δ-1 protein in a large cohort of european patients with primary absence epilepsy. Eroglu C et al., 2009, Cell, 139:380-92. Zaman T et al., 2011, Neuron 70:95-108.

Disclosures: **I. Santolini:** None. **M. Guiducci:** None. **T. Imbriglio:** None. **R. Celli:** None. **M. Cannella:** None. **M. Motolese:** None. **V. D'Amore:** None. **R. Gradini:** None. **G. van Luijtelaar:** None. **P. Parisi:** None. **F. Nicoletti:** None. **P. Striano:** None. **R.T. Ngomba:** None.

Poster

766. Epilepsy Networks and Channels

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Topic: C.07. Epilepsy

Support: Wellcome Trust (grants 102397 & 91882)

Title: Challenging the dogma: ethosuximide reduces natural and pentobarbital-induced spindles and non-REM sleep

Authors: L. J. BARUCHIN, M. VENZI, G. DI GIOVANNI, *V. CRUNELLI;
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Abstract: The occurrence of absence seizures (ASs), non-convulsive seizures characterized by EEG spike-and-wave discharges (SWDs) concomitant with impairment of consciousness, is strictly dependent on the patient arousal state, i.e. they most commonly emerge during quiet wakefulness but are relatively rare during active wakefulness and non-REM (NREM) sleep. Ethosuximide (ETX), a gold-standard anti-absence drug, is effective in 50% of patients under mono-therapy and abolishes ASs in all well-established experimental AS models. Thus, it is generally believed that ETX ability to block ASs is a necessary feature to validate new AS models. Indeed, in some instances, this pharmacological validation (i.e. the predictive validity) has become prevalent in defining a new model, often disregarding careful characterization of the EEG and behaviour (i.e. the face validity). This postulate is based on two assumptions: 1) ETX effect is specific to SWDs, i.e. ETX does not affect other brain oscillations; 2) ETX effect is specific to the mechanism of AS generation and is not mediated by other effects, such as changes in the arousal/sleep states, which could indirectly modulate SWD expression. Further complication arises from the fact that one hypothesis of the generation of SWDs is that they represent 'perverted' sleep spindles (0.5-3 sec oscillations with a frequency, 7-14 Hz, similar to experimental SWDs). In order to clarify these issues, we investigated the effect of ETX on natural and pentobarbital (PB)-induced spindles and NREM sleep in freely-moving Wistar rats implanted with fronto-parietal EEG and neck EMG electrodes. ETX (150 mg/kg i.p.) halved the time spent in NREM sleep, from 28±2% in saline pretreated and 56±2% in PB-pretreated rats to 11±1%($p<0.01$) and 28±6% ($p<0.01$; n=8 rats), respectively. Similarly, the number of spindles recorded over a two-hour period was decreased following ETX injection from 81±19 and 194±32 in saline- and PB-pretreated rats to 26±9 ($p<0.05$) and 73±18($p<0.01$), respectively. ETX also increased the spindle peak-to-peak amplitude, attenuated the increase of spindle frequency induced by PB, and shortened spindle duration from 963±18msec to 840±26msec in saline pretreated rats. A lower dose of ETX (50 mg/kg i.p.) produced smaller reductions than the higher dose on spindle and NREM sleep parameters but decreased spindle peak-to-peak amplitude. These results show that ETX has a strong effect on NREM sleep and sleep spindles, two thalamocortical-dependent brain activities. Current work is directly comparing ETX effects on SWDs, NREM sleep and spindles in AS models.

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Poster

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Topic: C.07. Epilepsy

Support: NSF Grant 1264948

Title: Glial waves during seizures - coupled or uncoupled with neurovascular activity?

Authors: *H. MA[1,2], A. G. S. DANIEL[1], P. LAFFONT[1,3], M. ZHAO[1,2], T. H. SCHWARTZ[1,2]; [1]Dept Neurolog. Surgery, [2]Feil Family Brain and Mind Res. Inst., Weill Cornell Med. Col., New York, NY; [3]The Browning Sch., New York, NY

Abstract: Background: Neuronal and glial activity are thought to coordinate regional blood flow through a complex sequence of events. During normal sensory processing, these events appear to be coupled in space and time. Using a 4-AP injection into rat cerebral cortex and simultaneous voltage sensitive and intrinsic signal (IS) wide-field imaging, we have previously shown that ictal events are coupled in space, but not time, with perfusion. Although glia are a key component in neurovascular coupling, wide-field imaging of glial waves during seizures has not been investigated. Methods: Using calcium dyes, either OGB-1, which can be filtered to image glia (1Hz), or the calcium dye Rhod-2, which stains only astrocytes, along with IS and local field potentials, we were able to measure each compartment of the neurovascular unit through a wide area of *in vivo* rat neocortex during seizure onset and evolution. Results: A clear glial wave which began focally and spread across the cortex occurred simultaneous with each ictal event. However, glial waves propagated 43% further (4.3±1.3 mm) than CBV changes (3.0 ± 1.0 mm, t-test, p=0.0013). Despite widely varying seizure durations (10-70s, 43.5±17.6 s), the duration of astrocytic activation remained more constant (10-40s, 23.6±6.5 s) and did not significantly correlate with the duration of the seizures (n = 25 seizures from 4 rats, r = 0.28, p = 0.18). The hemodynamic change, on the other hand, lasted longer than both the astrocytic and neuronal activity in all trials (54.5±17.7 s, p <0.01). Moreover, glial waves were significantly delayed in onset compared with hemodynamic waves (2.4±1.1 s versus 0.8±1.0s respectively, p<0.01). Our results suggest that during ictal events, each compartment in the neurovascular unit displays a unique spatiotemporal onset and evolution. Conclusions: Although clearly coupled in a macro-global scale i.e. similar number of events in a similar region of cortex, they are uncoupled on a micro-detailed scale. In spite of rapidly propagating multidirectional subthreshold neuronal waves of varying duration, glial activity is characterized by a more homogeneous slowly propagating wave that extends well beyond the limits of the neuronal or perfusion changes,

having a more constant predictable duration. These results call into question the putative essential role of astrocytes in ictal neurovascular coupling.

Disclosures: H. Ma: None. **A.G.S. Daniel:** None. **P. Laffont:** None. **M. Zhao:** None. **T.H. Schwartz:** None.

Poster

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INDO SWISS PPP PILOT PROGRAMME

Fluid Research Grant, Christian Medical College, Vellore.

Title: Two distinct ictal onset patterns in hippocampal CA1 subfield *in vitro*: A potential therapeutic role for oxytocin in controlling seizures

Authors: *D. SUBRAMANIAN[1], E. N. PRALONG[2], R. T. DANIEL[2], A. G. CHACKO[1], R. STOOP[3], K. S. BABU[1];
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Abstract: Pharmacological interventions in temporal lobe epilepsy have been notoriously unsuccessful up to now. Although effective in the beginning of the treatment, drug resistance often develops and previously successful drugs do not further work. The development of new pharmacological treatments is importantly guided by epileptiform mechanisms that are identified in *in vitro* slice models, but that may not necessarily reflect the precise human epileptic pathology. We here show in horizontal slices of the hippocampus prepared from 4-8 weeks old wistar rats, a new transitional mechanism of epileptiform activity in CA1 which was initially driven by glutamatergic inputs from the CA3, but then developed independently based upon GABAergic synaptic transmission. Thus, within thirty minutes after incubation in artificial cerebrospinal fluid containing 8.5 mM KCl and 1.2 mM CaCl2, we found the development in the CA1 of ictal-like epileptiform discharges with duration of 112 ± 3 sec, appearing every 186±4 sec and that could be blocked by AMPA and NMDA receptor antagonists. Around sixty minutes after incubation, a new type of activity appeared in the CA1 region, consisting of shorter

duration bursts (3.9±0.2 sec) in the gamma frequency range. Anatomical isolation of the CA1 from the CA3 abolished the long-duration ictal-like discharges in the CA1, allowing the short duration bursts to appear at shorter intervals of 53 ±1 s. Their activity was not affected by AMPA nor NMDA receptor antagonists but was effectively blocked by the GABA(A) receptor antagonist bicuculline. In addition, they were also significantly suppressed by the NKCC1 blocker bumetanide (20 μM) suggesting a change in chloride equilibrium potential to underlie their generation. Interestingly, the oxytocin agonist [Thr4, Gly7] oxytocin (TGOT, 0.4 μM), recently shown able to correct changes in the Cl- equilibrium potential, also suppressed the ictal-like discharges in these isolated CA1 mini-slices. Taken together, our findings reveal two different mechanisms of ictal onset in hippocampal CA1 region, one driven by glutamatergic input from CA3 and a second developed independently in CA1 by inhibitory neurons. This sequence of events reveals potential reasons why previous GABAergic enhancers may not function adequately in epileptiform tissue as they would enhance rather than decrease ictal activity. At the same time they provide a rationale and new model for testing efficacy of new anti-epileptic treatments such as oxytocin.

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Poster

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Title: Functional connectivity analysis of epileptic neural networks with inhibition

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Abstract: Fundamental insights into the dynamics of neural networks are being gleaned from graph analytic approaches. Simulations of various network topologies have shown that small

world networks (in which a few cells, from a predominantly locally-connected network, have long range connections) are a highly efficient architecture for communicating information. In experimental studies, however, anatomical connectivity of neuronal networks is seldom known. Instead, “functional connectivity” can be measured by quantifying correlated activity among recorded cells. Studies of functional connectivity have largely focused on identifying clusters of positively coupled cells (i.e. excitatory connections). Biological neuronal networks include inhibitory interneurons, which inhibit postsynaptic targets and thereby restructure functional network connectivity in a time and activity-dependent manner. Here we use windowed analysis of calcium imaging data to characterize the transitions in functional network architecture in hippocampal organotypic slice cultures, which are spontaneously epileptic, and cycle through interictal, pre-ictal, ictal, and post-ictal states. We found 1) Small-world network topology transiently emerges in CA1 pyramidal cells during epochs associated with pre-ictal disinhibition. 2) In whole-slice calcium imaging experiments in which interneurons are distinguished by flourescent tags, we computed the peak absolute value of cross-correlation between all pairs of neurons imaged and defined negative peaks as inhibitory. Preliminary data indicate that, during interictal states of relative inactivity, interneurons are most commonly negatively correlated to principal neurons (I-E), whereas principal cells tended to be positively correlated with other principal cells (E-E). We can now use this approach to characterize both short-term dynamical changes in functional inhibitory networks preceding seizure onset, and the longer-term reorganization of inhibitory circuits during post-traumatic epileptogenesis.

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Poster

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NRF-2011-0028772 by the Korea government (MSIP)

Title: Optogenetic mapping of functional connectivity in freely-moving mice via insertable wrapping electrode array beneath the skull (iWEABS)

Authors: *A. PARK[1], S. LEE[2], C. LEE[3], J. KIM[1], H. LEE[2], S.-B. PAIK[3], K. LEE[2], D. KIM[1]; [1]Biol. Sci., [2]Materials Sci. and Engin., [3]Bio and Brain Engin., KAIST (Korea Advanced Inst. of Sci. and Tec, Daejeon, Korea, Republic of

Abstract: Mapping the wide-ranging neuronal interactions across cortical areas during behaviors has been challenging. Although flexible electrode array covering the cortical surface have recently emerged as a solution, it requires the removal of the skull leading to gross damages to the brain. Here, we developed an insertable wrapping electrode array beneath the skull (iWEABS), an electrocorticogram (ECoG) system optimized for recording activity from sizable cortical areas in freely-moving mice. The iWEABS is designed to be inserted through a small cranial window and stably attached on the cortical surface in mice. Using the iWEABS system, we measured global cortical activities in freely-moving states. Furthermore, we reveal that the iWEABS system is highly compatible with the optogenetic mapping of cortical interactions during absence seizures. Therefore, the iWEABS system can be a standard method for the study of expansive functional connectivity in mice.

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Poster

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Title: Differential dominant negative suppression of gabrg2 nonsense epilepsy mutations and the protein structural basis

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Abstract: Mutations in GABAA receptor subunit genes (GABRs) are frequently associated with epilepsy, and nonsense mutations in GABRG2 are associated with various kinds of epilepsy syndromes including febrile seizures, childhood absence epilepsy, generalized tonic clonic seizures and the most severe form epileptic encephalopathy like Dravet syndrome. The molecular basis for the phenotypic heterogeneity of these truncation mutations is not clear. In this study, we focused on three nonsense mutations in GABRG2 (GABRG2(R136X), GABRG2(Q390X) and GABRG2(W429X)) associated with epilepsies of different severities. With structural modeling, flow cytometry and biochemical approaches in combination with lifted whole cell patch clamp recordings, we demonstrated that the truncation mutations all had absent to minimal surface expression of the mutant subunit and unchanged or reduced wild-type partnering subunits expression. The GABA evoked- current amplitudes from cells cotransfected with α1β2γ2(R136X), α1β2γ2(Q390X) and α1β2γ2(W429X) subunits were reduced compared to the currents from α1β2γ2 subunits but with different level of reduction. The different mutant subunits had different steady state levels of mutant protein expression. The structural modeling and structure-based analysis indicated that the wild-type γ2 subunit surface was naturally hydrophobic, which is suitable to be buried in membrane The different γ2 subunits adopted different conformations, and the hydrophobicity scores were different among these misfolded subunits. In the docking study, the mutant γ2(Q390X) subunits formed protein specific or nonspecific stable protein dimers with themselves or other proteins while γ2(R136X) subunits could not form dimers with other partnering subunits but could dimerize with themselves. The γ2(W429X) subunits also dimerized with themselves but the protein conformation was similar to the wild-type γ2 subunit protein.

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Poster

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Topic: C.07. Epilepsy

Support: NIH Grant NS090364

Title: Modeling SCN8A mutant epilepsy in patient-derived cortical and peripheral neurons

Authors: *A. M. TIDBALL[1], L. LOPEZ-SANTIAGO[2], X. DU[1], K. GLANOWSKA[1], L. ISOM[2], J. M. PARENT[1];
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Abstract: De novo mutations are major contributors to the development of childhood epileptic encephalopathies (CEEs) such as Dravet syndrome, infantile spasms, and Lennox-Gastaut syndrome (LGS) (Carvill et al 2013; O'Brien et al 2013; Epi4K Consortium 2013). CEEs comprise some of the most severe and pharmaco-resistant classes of epilepsy (Chiron and Dulac 2011). Mutations in the SCN8A gene have recently been shown to be causative for cases of infantile spasm, LGS, and CEE (Veeramah et al 2012; O'Brien et al 2013). CEEs often lead to intellectual and physical disabilities in later life as well as high rates of SUDEP (Sudden Unexpected Death in Epilepsy). These mutations have been shown to result in both gain-of-function and loss-of-function mutations (Veeramah et al 2012; Blanchard et al 2015). The goal of this research project is to use patient-derived cells to characterize electrophysiology alterations caused by SCN8A mutations associated with early-onset epilepsy and develop a novel platform for identifying effective pharmacological agents for this debilitating disease. SCN8A, which encodes for the voltage-gated sodium channel is expressed in both the PNS and CNS, where it is the most abundant Nav channel. We have identified two CEE patients with missense mutations in SCN8A (Arg1872>Leu and Val1592>Leu). Fibroblasts from the patients' skin biopsies were reprogrammed into induced pluripotent stem cells (iPSCs). These iPSCs have subsequently been differentiated by two different protocols into neurons expressing cortical excitatory and peripheral markers respectively. These cells are being used to first deduce the effect the Nav1.6 mutations have on electrophysiological properties of the neurons, particularly sodium current density and persistent sodium current. We hypothesize that these mutations will increase both of these measures leading to hyperexcitability of the neurons as has been shown in the majority of other SCN8A mutations in mouse models and heterologous systems. We have also used a multielectrode array platform (Axion Biosystems) to measure spontaneous activity. Cortical neurons from three patient lines all show increased spontaneous activity and burst activity compared to one human iPSC-derived neuronal control line. Future studies will involve culturing cortical and peripheral neurons, as well as cardiac myocytes, on MEAs to test known antiepileptic drugs and screen drug libraries for amelioration of hyperexcitable phenotypes. This work will shed light on SCN8A CEE seizure and SUDEP mechanisms and should provide lead compounds for clinical testing.

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Poster

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Title: Kinetic models of Slack channel function confirm cooperative gating in Slack-associated epilepsy mutations

Authors: *I. H. QURAISHI[1], J. KRONENGOLD[2], L. K. KACZMAREK[2,3];
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Abstract: Mutations in Slack (KCNT1) Na^+-activated K^+ channels lead to a spectrum of childhood epilepsy syndromes including malignant migrating partial seizures of infancy and autosomal dominant nocturnal frontal lobe epilepsy. These mutations increase Slack current amplitude at the whole cell level, as has been demonstrated in oocytes expressing the mutant channels. At the single channel level, only minor changes in gating of the mutants are observed in patches containing a low (1-3) number of channels. In contrast, in clusters of 4 or more channels, the open probability is very much greater than that of wild type channels. The distribution of open and closed states in such clusters deviates very strongly from the binomial expectation of independently gating channels. To confirm cooperativity in such clusters, we developed a nonlinear kinetic model of Slack channel gating. We compared the predictions of the model for open times and opening and closing latencies with data obtained in experimental channel recordings. For these comparisons, multichannel patch recordings were selected which appeared to have cooperativity based on comparison of channel opening histograms to recordings in patches with fewer channels. We first made a model with independent gating of channels in a cluster. The overall increase in channel opening in clusters could readily be fit by simply assuming that opening rate of the channels in a cluster was increased over that of single channels. This independently gating model however completely failed to predict conditional opening and closing latencies. In the second model, the kinetic parameters were dependent on the number of neighboring open channels. This cooperative gating model provided a much closer fit to the observed data. The dependence of the opening rate constant on the number of open channels was best fit by a saturable function. These results offer further evidence that the dysfunction in epilepsy-causing Slack mutations are depends on interactions between

neighboring channels. Inter-channel interactions could therefore be a potential therapeutic target in Slack-associated epilepsies.

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Poster

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Support: French Research Ministry

Title: Neuronal network dysfunctions at the early stage of epileptogenesis in a genetic model of absence epilepsy

Authors: *G. JARRE, D. RUDRAUF, A. DEPAULIS, I. GUILLEMAIN;
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Abstract: Epilepsies are characterized by recurrent seizures caused by a hyper-synchronicity and hyper-excitability of neuronal networks. Although the dynamics of these networks have often been studied in epilepsy, little is known about the epileptogenic process, i.e. epileptogenesis, in which recurring epileptic discharges progressively emerge. In genetic epilepsies, this process often takes place during brain maturation as in absence epilepsy, a childhood syndrome characterized by non-convulsive generalized seizures. In the Genetic Absence Epilepsy Rat from Strasbourg (GAERS), spontaneous seizures are characterized by spike-and-wave discharges (SWD) on the EEG and are initiated in the somatosensory cortex (SSC). We recently recorded spontaneous abnormal oscillations after the 15th post natal day (P15) which preceded the first SWD occurring at P25. Intracellular recordings during the epileptogenesis process suggest a strengthening of the synaptic activity in the network, potentially reflecting underlying network dysfunctions. Here, we aimed at understanding how the SSC's neuronal networks contribute to the emergence of SWD early on during epileptogenesis. We used *in vivo* two-photon calcium imaging in GAERS and age-matched control Wistar rats pups (P15-P19), under slight sedation (neurolept-analgesia), in order to simultaneously record calcium activity from multiple neurons in layer 2-3 of the SSC. We found that, GAERS SSC neurons were already hyperactive, with more frequent and longer calcium onsets than in controls. Analysis of functional connectivity within the network based on normalized pairwise correlation between neurons demonstrated a higher percentage of functionally connected neurons in GAERS vs controls. Overall, the values

of the correlations appeared smaller in GAERS, but they decreased as a function of between-neuron distance significantly more slowly in GAERS than in controls (over about 200µm vs 100µm). Such connectivity pattern remained unaltered after normalizing neuronal activity in GAERS pups using an acute injection of ethosuximide, an anti-absence drug. This supported the hypothesis that the dysfunction was related to an abnormal intrinsic connectivity rather than a neuronal hyperactivity per se. Altogether, these findings suggest the existence of a functional anomaly of the SSC neuronal network at the early stage of absence epileptogenesis, before SWD onset. In follow up analysis, based on multidimensional clustering techniques, clusters of neurons sharing similar activities could be quantified and characterized in order to better understand the physiopathology of absence epilepsy in the GAERS model.

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Poster

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Title: The human GluN2A mutation P552R enhances NMDA receptor function and promotes neurotoxicity

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Abstract: NMDA receptors mediate a slow, Ca2+ permeable component of excitatory synaptic transmission in the central nervous system. Overactivation of these receptors can be harmful due to swelling, which is secondary to influx of Na+, and excessive accumulation of intracellular Ca2+. Recently, mutations in the genes encoding NMDA receptor subunits have been identified in a number of cases of developmental delay and epilepsy, with mutations in the GRIN2A gene encoding the GluN2A subunit being most common. Here we describe a mutation in GRIN2A that leads to an amino acid change in the pre-M1 gating region (GluN2A-P552R), and was identified in a patient with developmental delay and epilepsy (de Ligt et al., N Engl J Med 367:1921-1929, 2012). We evaluated the functional effects of this mutation on recombinant GluN1/GluN2A receptors, and found that the potency of both glutamate (EC50 WT 3.3 uM, P552R 0.37 uM, n=9-13 oocytes) and glycine (EC50 WT 1.2 uM, P552R 0.06 uM, n=10 oocytes) increased ~10-fold without a change in open probability (n=12-17 oocytes). The time course of the response to rapid application of glutamate was dramatically slowed, with the 10-90% rise time increased 50-fold from 10 to 576 ms, and the weighted time constant describing the deactivation time course following rapid removal of glutamate increased from 45 to 794 ms (n=5-6 cells). As a result of these changes, charge transfer in response to brief synaptic-like exposure to glutamate increased more than 20-fold, raising the possibility that this mutation leads to neurotoxicity. To assess this possibility, we transfected rat cortical neuronal cultures with GFP, GFP+wild-type GluN2A, or GFP+GluN2A-P552R at 21 days *in vitro*. Our preliminary results suggest that neuronal morphology was unchanged between GFP and GFP+GluN2A-transfected neurons, however transfection of GFP+GluN2A-P552R produced extensive swelling within the dendrites. Quantification of co-transfected luciferase suggested mutant GluN2A-P552R increased neuronal death. These data are consistent with the idea that activation of GluN2A-P552R could compromise neuronal health, and may contribute to the neuropathology observed in this patient. These results also suggest that the pre-M1 helix contributes to the process of channel gating.

Disclosures: **S.F. Traynelis:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeurOp Inc (SFT). F. Consulting Fees (e.g., advisory boards); NeurOp Inc, Janssen (SFT). **K.K. Ogden:** None. **W. Chen:** None. **A. Tankovic:** None. **E. Aizenman:** None. **K.B. Hansen:** None. **H. Yuan:** None.

Poster

766. Epilepsy Networks and Channels

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 766.25/C78

Topic: C.07. Epilepsy

Support: CIHR MOP-136969

CIHR MOP-136967

NSERC 298475

Title: Age-dependency of trauma-induced epilepsy in mice

Authors: *S. SOLTANI[1], J. SEIGNEUR[2], S. CHAUVETTE[2], I. TIMOFEEV[1];
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Abstract: Traumatic brain injury is a major risk factor for epileptogenesis. Cortical trauma leads to paroxysmal activity within 24 hours in up to 80% of patients and stops within a 48-hour period. Trauma-induced epileptogenesis (TIE) starts from that point and has unknown mechanisms leading to network reorganization and epilepsy. Because mechanisms of TIE are unknown, there is no treatment to prevent epileptogenesis. Understanding and preventing TIE will prevent epilepsy. We hypothesized that a partial deafferentation leads to a drop in excitability of the affected area. Brain then employs a variety of mechanisms to upregulate neuronal excitability (axonal sprouting, synaptic upregulation of excitatory and down-regulation of inhibitory synapses, alteration of intrinsic neuronal currents, ...). A reliable model of TIE is cortical deafferentation (undercut) and our group recently proposed that TIE is age-dependent because cats of unknown age developed epilepsy in about 70% of cases, while young cats did not. We aimed to verify this hypothesis of age-dependency in mice. We hypothesized that a 'plastic' brain (young animals) would restore excitability to a normal level. In a 'less plastic brain' (adult or old animals) this increase in excitability would be poorly controlled and lead to the development of epilepsy. The methodologies included aseptic surgeries, chronic electrographic recordings, and cortical undercut. We performed undercut in the somatosensory area in wild-type (C57BL/6) mice of different ages (young and old) under isoflurane anesthesia. Mice were implanted with LFP electrodes in different cortical areas and EMG to identify behavioral states. The electrographic activities of these mice were recorded continuously for at least two months or until they developed epilepsy. Almost all animals generated acute seizures of variable morphology within the first 10 hours after the lesion. In young animals, only isolated interictal spikes, but not seizures were recorded afterwards. In the following weeks, all old mice revealed recurrent seizure activities of different types. The most common type was 8-16 Hz spindle-like oscillations in the frontal cortex accompanied with an increase in the muscle tone and either body freezing or rhythmic contractions. In some animals, lower frequency (3-6 Hz) seizures were generalized and accompanied by behavioral freezing and low muscle tone or by rhythmic muscle and body contractions. The low frequency (1.5-3 Hz) seizures were accompanied with rhythmic muscle contractions. We conclude that TIE is age-dependent and it is likely due to an uncontrolled up-regulation of excitability in adult animals.

Disclosures: **S. Soltani:** None. **J. Seigneur:** None. **S. Chauvette:** None. **I. Timofeev:** None.

Poster

767. Neurotoxicity: Neuroprotective Mechanisms

Location: Hall A

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Program#/Poster#: 767.01/C79

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: minority recruitment supple ment at UIC to Dr. Testai

NIH Grant R01-NS063279 to Dr. Pelligrino

Title: FTY720 preserves blood-brain barrier integrity and restricts brain edema in rats subjected to subarachnoid hemorrhage

Authors: B. CHANGYALEKET[1], F. ZHAI[1], A. MUHAMMAD[2], C. PAISANSATHAN[1], D. PELLIGRINO[1], *H.-L. XU[1], F. TESTAI[2];
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Abstract: Our recent study indicated that, in rats subjected to subarachnoid hemorrhage (SAH), the treatment with FTY720, a sphingosine 1-phosphate receptor modulator, was associated with a restriction of neuroinflammatory reaction, preserved cerebrovascular dilating function, and improved neurological outcome. The blood-brain barrier (BBB) disruption that leads to consequent edema formation has been recognized as one of the major contributors to SAH-related early brain injury. The core objective of the present study was to test the hypothesis that the neuroprotective effect of FTY720 is, at least partially, derived from its action on preserving BBB and restricting brain edema. The experiments were guided by 2 specific aims testing (1) effect of FTY720 on SAH-induced loss of BBB integrity; and (2) effect of FTY720 on SAH-associated brain edema. SAH was established using a rat anterior cerebral artery perforation model. Animals were randomized into three groups: (1) sham surgical control; (2) SAH rats treated with vehicle solution; and (3) SAH rats treated with FTY720. FTY720 was applied via an intraperitoneal route at 3h post SAH. Brain samples were collected at 48 h post SAH to determine BBB integrity and brain edema. BBB integrity was evaluated based on the cortical distribution of Evan's blue (EB) and the immunochemistry stain of tight junction proteins (ZO-1 and occludin). Brain edema was expressed as brain water content using the weight/dry method. Compared to sham surgical group, the permeability of BBB to EB was elevated significantly in the vehicle-treated SAH animals (12.96±3.14 μg/g tissue, vs 3.20±2.12 μg/g tissue in the sham

surgical group). FTY720 markedly restricted EB interstitial accumulation (6.96±2.83 μg/g tissue). Immunochemistry staining revealed that both ZO-1 and occludin were strongly expressed and heavily concentrated along with the cerebral microvessels in sham group. This expression pattern, however, was diminished at 48 h post-SAH. FTY720 partially restored the expression of these proteins. SAH was accompanied by a severe brain edema (SAH: 82.50±0.94%, vs sham: 79.38±0.37%), which was normalized by the presence of FTY720 (79.63±0.72 %). These results suggest that the attenuation of SAH-associated BBB disruption and brain edema accounts for the neuroprotective effect of FTY720.

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Poster

767. Neurotoxicity: Neuroprotective Mechanisms

Location: Hall A

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Program#/Poster#: 767.02/C80

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Title: Attenuation of methamphetamine-induced neurotoxicity by dl-3-n-butylphthalide in sh-sy5y neuroblastoma cell line

Authors: J. ZHAO[1], *H. (. XIONG[2], J. LIU[2], Y. LIU[1], X. ZHANG[1], H. LI[1], H. LIU[2]; [1]Dept. of Neurol., Taian City Central Hosp., Taian, China; [2]Univ. of Nebraska Med. Ctr., Omaha, NE

Abstract: Methamphetamine (Meth) is a highly addictive drug and its abuse is associated with neural cell injury and loss. Currently, there are no efficacious therapies to treat Meth-induced neuronal injury as the mechanisms underlying Meth-associated neuronal injury are poorly understood. Thus, research in elucidating the mechanisms and identifying potential therapeutic interventions is imperative. In the present study, we investigated how Meth causes neural cell injury and tested protective effects of DL-3-n-Butylphthalide (NBP), a synthetic compound based on L-3-n-Butylphthalide which was isolated from seeds of Apium graveolens, in SH-SY5Y Neuroblastoma cell Line. Treatment of SH-SY5Y cells with Meth produced a reduction of cell viability in a dose-dependent manner as detected by PI staining and MTT assay. The Meth-induced reduction of cell viability was significantly attenuated by pretreatment of SH-SY5Y cells with NBP. Western blotting studies revealed that Meth reduced cell viability by upregulation of cleaved-caspase-3 and NBP partially reversed the Meth-associated upregulation of cleaved-caspase-3, resulting in neuroprotective activity, indicating that NBP attenuates Meth-

induced neural cell injury by down-regulation of Meth-associated caspase 3 activation. Our results suggest that NBP could be a potential therapeutic agent for Meth-induced neural cell injury.

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Poster

767. Neurotoxicity: Neuroprotective Mechanisms

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: USDA Intramural Grant

Title: Blueberries affect neuroinflammation and cognition differentially depending on individual cognitive baseline status

Authors: N. THANGTHAENG, M. G. MILLER, S. M. POULOSE, D. F. BIELINSKI, D. R. FISHER, *B. SHUKITT-HALE;
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Abstract: Aging and neurodegenerative diseases are thought to be the results of prolonged effects of oxidative stress and inflammation. Previously, we have shown that daily supplementation of blueberries (BBs) was able to reverse age-related deficits in behavioral and neuronal function in aged rats. However, it is unclear whether BB will be more beneficial to one subset of the population compared to another, or if the beneficial effects are a global phenomenon where everyone benefits equally. Because there are various degrees of age-related cognitive decline and inflammation status observed in the general population, it is possible that daily BB supplementation would have differential effects dependent on baseline cognitive performance. To examine the effect of individual differences on the efficacy of dietary BB, aged rats (17 mo old) were assessed for cognitive status via the radial arm water maze (RAWM) and divided into good, average, and poor performers based on reference (RM) and working memory (WM) errors. Half of the rats in each cognitive group were then fed a control or a 2% BB diet for 8 weeks, before being re-tested in RAWM. Serum samples were collected pre-diet and at the end of the study to assess inflammation. The control-fed good performers committed more WM and RM errors in the post-test than pre-test ($p<0.05$), while the BB-fed good performers showed no change. Latency in the RAWM was significantly ($p<0.05$) reduced in the BB-fed poor

performers from pre- to post-test. A subsequent *in vitro* study using the serum showed that cognitive performance is associated with innate anti-inflammation capability, and BB supplementation further enhanced this capability. Behavioral findings reflect the individual rat's neuroinflammation status. Based on these findings, daily consumption of BB may reverse some age-related deficits in cognition, as well as preserve function among those with intact cognitive ability, especially in those with increased inflammation and poor cognitive status.

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Poster

767. Neurotoxicity: Neuroprotective Mechanisms

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Program#/Poster#: 767.04/C82

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: USDA Intramural Grant

California Walnut Commission

Title: Aging and walnut-rich diet supplementation affects the expression of immediate-early genes in critical brain regions

Authors: S. M. POULOSE[1], *D. F. BIELINSKI[1], J. W. CROTT[2], A. J. ROE[1], N. THANGTHAENG[1], B. SHUKITT-HALE[1];
[1]Neurosci. & Aging Lab., [2]Vitamins and Carcinogenesis, USDA Human Nutr. Res. Ctr, Tufts Univ., Boston, MA

Abstract: Emerging evidence indicates a direct link between age-associated changes in epigenetic mechanisms and onset of neurodegenerative diseases, and that these genomic modulations are directly affected by diet. Diets deficient in folate, choline and methionine, or the trace elements zinc and selenium, are reported to induce DNA hypomethylation and are linked to aberrant gene transcription. In a cognitively healthy adult, transcription of immediate-early genes (IEGs) is essential in memory formation and synaptic plasticity. In the current study, we investigated the effect of walnut diets, which are rich in polyunsaturated fatty acids and nutrients such as folate, selenium, magnesium and polyphenolics, on epigenetic mechanisms in critical regions of the brain. Young (3 months, n=30, 10/group) and old (19 months, n=45, 15/group) male Fischer 344 rats were supplemented with control (0%), 6% or 9% walnut diets for 10

weeks. All animals were tested on the radial arm water maze (RAWM) which measures spatial learning and memory. Age-related deficits in cognitive behavior were exhibited in the RAWM. The 9% walnut diet improved performance in the RAWM in both young and old rats. In hippocampus, target gene expression using the comparative CT (ΔΔCT) method revealed that differential regulation of IEG signaling exists for the different walnut treatments. Significant aging effects were observed for the expression of BDNF, ARC, EGR1 and AKT1 genes. The most significant difference between 6% and 9% WN was their effect on the RELN and EGR1 genes. BDNF increased among old animals fed with WN diet. In frontal cortex, expressions of target genes were affected by both age as well as diet. Significant increases in the transcript levels of zif268 or EGR among the 9% WN group could be a factor for the improved memory in that group. Benefits observed with regard to reference memory among animals fed with the 9% walnut diet could possibly be linked to the higher transcript levels of EGR1 in the frontal cortex, which is involved in cognition, long-term memory, and learning.

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Poster

767. Neurotoxicity: Neuroprotective Mechanisms

Location: Hall A

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Program#/Poster#: 767.05/C83

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: USDA Intramural Grant

California Strawberry Commission

Title: Effects of strawberry supplementation on mobility and cognition in older adults

Authors: M. G. MILLER, *N. THANGTHAENG, T. M. SCOTT, B. SHUKITT-HALE; Neurosci. and Aging, Jean Mayer USDA Human Nutr. Res. Ctr. On Aging At Tufts Univ., Boston, MA

Abstract: During aging, functional changes in the central and peripheral nervous system can alter mobility and cognition - in some cases leading to early cognitive decline, disability, or injurious falls among older adults. Previously, we have shown that two months of dietary supplementation with berry fruit can reverse several parameters of brain aging, as well as age-related motor and cognitive deficits, when fed to aged rats (19 months old). The present study investigated the effects of 3 months of dietary supplementation with strawberry (12g twice a day, equivalent to approx. 2 cups/day fresh strawberry) or a seemingly identical, isocaloric placebo powder on healthy older men and women (60-75 years old). Participants completed a battery of balance, gait, and cognitive tasks at day 0, 45, and 90 of supplementation. Dietary supplementation with strawberry attenuated some aspects of declining mobility and cognition in older adults. Including berry fruit in the diet of healthy older adults may therefore be one means of combating age-related functional declines.

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Poster

767. Neurotoxicity: Neuroprotective Mechanisms

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 767.06/C84

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Title: Effect of progesterone treatment in streptozotocin-induced diabetic neuropathy

Authors: *S. YOUSUF[1], F. ATIF[1], M. C. PRUNTY[2], J. WANG[1], D. G. STEIN[1];
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Abstract: Diabetic neuropathy (DN) is the common name for nerve damage caused by diabetes mellitus. The diabetic brain has been little studied and its possible dysfunctions remain to be identified. Progesterone (PROG) is a neurosteroid with well-established neuroprotective properties. We investigated the effect of PROG on DN-induced changes in brain function. DN was induced in male Sprague Dawley rats by intraperitoneal administration of streptozotocin (STZ) (60 mg/kg, b.w.) for 5 weeks. The animals were divided into sham control (Sham, n=8); streptozotocin (STZ, n=8) -treated and STZ+PROG (STZ+PROG, 8 mg/kg for 17 days with tapering, n=8) -treated groups. PROG treatment was started after hyperglycemia was confirmed

3 days after administering STZ. Body weight and blood sugar were evaluated weekly for 5 weeks. At the end of week 5, spontaneous locomotor activity of the animals was assessed. Various markers for angiogenesis (vascular endothelial growth factor (VEGF)), inflammation (IL-6) and injury (CD11b, NG2, IL-6, COX2 and matrix metalloproteinaise-2 (MMP-2)) were evaluated in brain, spinal cord and sciatic nerve tissues. We examined changes in intraepidermal nerve fibers (IENFs) by using the antibody PGP 9 in the foot pads to evaluate whether PROG has any effect on nerve fiber regeneration. PROG treatment did not lead to any significant improvement in body weight by the end of 5 weeks. Blood glucose values were found to be significantly ($p<0.05$) decreased in the PROG-treated group at the end of week 5 compared to the STZ group. The STZ group covered significantly ($p<0.05$) more distance than sham or the PROG+STZ group, a finding we attribute to hyperactivity due to diabetes. Reduced PGP9 and IENF densities were found in the STZ group compared to sham, whereas PROG treatments led to an increase in IENF densities. Significant changes were seen in the STZ group in expression of VEGF, CD11b, NG2, IL-6, COX2 and MMP-2. PROG treatment reduced these changes, thereby limiting further DN damage. Based on our findings, we conclude that PROG might represent a safe and effective therapeutic for DN treatment. **Keywords:** Progesterone, Diabetic Neuropathy, IENF, Behavior

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Poster

767. Neurotoxicity: Neuroprotective Mechanisms

Location: Hall A

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Title: Neuroprotective effect of valproic acid in a neonate rat hypoxia model

Authors: *J. M. ORTEGA IBARRA, SR[1], S. J. LÓPEZ PÉREZ[2];
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Abstract: During neonate period the brain is particularly sensible to hypoxia. Neonate rats exposed to hypoxia showed apoptosis, neuronal projections loss and high extracellular glutamate. Valproic acid (VA) has been shown neuroprotection in experimental models of hypoxia. The goal of this study was to estimate the density of brain cells in 20 and 30 days old rats (DOR) subjected to hypoxia in the neonatal period, which received a daily dose of VPA until sacrifice. Sections of prefrontal cortex (PFC), dorsal striatum (DS), sustantia nigra pars compacta

(SNpc) and ventral tegmental area (VTA) were processed by immunohistochemistry whit NeuN/TH or GFAP antibodies. In hypoxic 20 DOR, a diminution of $NeuN^+$ cells in PFC was found (2131 ± 103 vs. 2338 ± 43 CTL vs hypoxia groups respectively), but higher cell number in the VA groups (2537 ± 81 vs CTL). In SNpc we found less TH^+ neurons in hypoxic animals vs CTL (215 ± 43 vs 242 ± 37 respectively) and higher cell count in VA group (331 ± 35 vs CTL). There were no differences in $NeuN^+/TH^+$ cells in DS and ATV. With respect to $GFAP^+$ cells in hypoxic PFC, a high amount than CTL was found (433 ± 18 vs. 348 ± 31 respectively), whereas the VA group did not show difference (227± 15 vs CTL). In the DS, hypoxia induced an increase, whereas AV treatment has the same level of CTL (443 ± 18, 223± 15 and 235 ± 31 respectively). SNpc from hypoxic animals also had more $GFAP^+$ cells than CTL (509 ± 13 vs 391 ± 42 respectively), and the VA treatment was associated with a smaller cells number (223 ± 15 vs CTL). In PFC of **30 DOR**, a decreased number of $NEuN^+$ cells was found (2336 ± 40 vs. 2175 ± 46 CTL vs hypoxia respectively) and an increase in the VA treated groups (2527 ± 37 vs. CTL). In the SNcp, TH^+ cells in hypoxic group were less than in CTL group (228 ± 35 vs 392 ± 24 respectively), whit a higher cell number in the VA treated group (414 ± 61 vs CTL). VTA of hypoxic group showed less TH^+ cells that CTL group (154 ± 35 vs. 224 ± 35 respectively); the VA treatment did not show differences with CTL. In SD no significant difference was found in $NEuN^+$ cells count neither whit hypoxia nor VA. About $GFAP^+$ cells in 30 DOR, SNpc showed more cells in hypoxic group than CTL (632 ± 31 vs 463 ± 57 respectively), and a diminution in the VA group (287± 6 vs CTL). In DS and VTA did not found any difference. Altogether these results indicates that hypoxia had a general deleterious effect on the density of the cell types analyzed heren and VA treatment attenuates cell loss and appears to prevent astrocytes proliferation, suggesting a neuroprotective effect in this neonatal hypoxia model. Support: UDG 221023

Disclosures: **J.M. Ortega Ibarra:** None. **S.J. López Pérez:** None.

Poster

767. Neurotoxicity: Neuroprotective Mechanisms

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Support: CAPES/DGU Grant 173/2008

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Title: Protective role of folic acid against glutamate-induced excitotoxicity in hippocampal slices is dependent on PI3K/AKT/GSK-3B/B-catenin pathway and inhibition of iNOS

Authors: ***M. MORETTI**[1], J. BUDNI[2], S. MOLZ[3], T. DAL-CIM[2], M. D. MARTÍN-DE-SAAVEDRA[4], J. EGEA[4], M. G. LÓPEZ[4], C. I. TASCA[2], A. L. S. RODRIGUES[2];
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Abstract: Introduction and objectives: Folic acid (folate) is a water-soluble vitamin important for neurological function. Since excitotoxicity induced by glutamate is a pathological event associated with different diseases, we investigated the putative protective role of folic acid on glutamate-induced hippocampal slices damage in rats as well as the intracellular signaling pathways involved in such effect. Methods: Hippocampal slices were isolated from adult male Wistar rats and incubated 1 h with 1 mM glutamate. When present, folic acid (1, 10 and 100 μM) was preincubated for 30 min. LY294002 (PI3K inhibitor, 30 μM) was added to the incubation medium 15 min before folic acid and maintained during the folic acid preincubation period. After glutamate incubation, slices were maintained in fresh culture medium without glutamate for an additional 6 h period. D-[3H]-aspartate release was determined through scintillation counting and cell viability was measured as MTT reduction. The phosphorylation of GSK-3β (Ser 9) and the immunocontent of β-catenin and iNOS were evaluated using western blot. Results: Hippocampal slices treated with folic acid (100 μM) had a significant reduction of cell death and D-[3H]-aspartate release induced by glutamate. The administration of LY294002h abolished the protective effects of folic acid against glutamate-induced cell damage and D-[3H]aspartate release. Six hours after glutamate insult, folic acid induced phosphorylation of GSK-3β and β-catenin expression in hippocampal slices of rats. In addition, glutamate-treated hippocampal slices exhibited increased iNOS immunocontent, an effect that was reversed by folic acid preincubation. Conclusions: The results of this study show that folic acid can protect hippocampal slices against glutamate-induced excitotoxicity through a mechanism that involves PI3K/Akt/GSK-3β/β-catenin pathway and inhibition of iNOS.

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Poster

767. Neurotoxicity: Neuroprotective Mechanisms

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: R01 AA020103

Title: Binge ethanol exposure increases the Kruppel-like factor 11-monoamine oxidase (MAO) pathway in rats: Examining the use of MAO inhibitors to prevent ethanol-induced brain injury

Authors: *J. W. DUNCAN[1], X. ZHANG[1], S. JOHNSON[1], C. UDEMGBA[1], N. WANG[1], S. HARRIS[1], X. OU[1], C. STOCKMEIER[1,3], J. WANG[1,2];
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Abstract: Alcohol misuse can result in devastating effects to the brain and behavior and is a major cause of morbidity worldwide. Binge drinking, in particular, induces several neurotoxic consequences, including oxidative stress and neurodegeneration. Because of these deleterious effects, drugs which prevent ethanol-induced detriment to brain could be very beneficial. We have observed an ethanol-responsive effect of the pro-apoptotic, Sp1-like transcription factor, Kruppel-like factor 11 (KLF11), and its transcriptional target, Monoamine Oxidase-B (MAO-B), in rodents exposed to a chronic ethanol model. Here, we examined whether the KLF11-MAO pathway is also upregulated in a binge ethanol rodent model and, further, whether administration of new generation Monoamine Oxidase Inhibitors (MAOIs) yielded some neuroprotective effects against ethanol as have been demonstrated in other neurodegenerative rodent models. Sprague-Dawley rats were administered N-propargylamine-containing MAOIs (Selegiline, Rasagiline, or M30) and fed ethanol by intragastric gavage following a modified 4-day Majchrowicz binge model. Binge ethanol rats demonstrated an increase in KLF11, both MAO isoforms, catalase, and caspase-3 expression compared to control rats. Moreover, Rasagiline and M30 significantly reduced the ethanol-mediated increase of KLF11, and M30 increased catalase expression in both control and binge ethanol rats. These results suggest an active ethanol-induced cell death mechanism involving the KLF11-MAO pathway in binge ethanol-treated rats and demonstrates some neuroprotective enhancement afforded by MAOI drug therapy. Further investigation of new generation MAOIs to improve ethanol-related brain injury outcomes is warranted. In addition, examining whether the pharmacotherapeutic effects of MAOIs persist during withdrawal of high concentrations of ethanol, as seen in alcohol poisoning, is of great interest due to its clinical relevance.

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Poster

767. Neurotoxicity: Neuroprotective Mechanisms

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 767.10/C88

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Title: Rosmarinic acid and carnosic acid display overlapping and distinct neuroprotective effects in cultured cerebellar granule neurons

Authors: *F. I. TARAM[1], E. IGNOWSKI[2], D. LINSEMAN[2];
[1]Biol., [2]Univ. of Denver, Denver, CO

Abstract: Neurodegeneration in the brain and spinal cord underlies many devastating diseases, such as amyotrophic lateral sclerosis (ALS), Alzheimer's disease, and Parkinson's disease. All of these disorders are characterized by the progressive loss of neurons in specific regions of the brain and/or spinal cord due to apoptosis, necrosis, or other forms of cell death. Oxidative and nitrosative stress, along with excitotoxicity and caspase activation, have been implicated as major pathways leading to cell death. Nutraceuticals (natural products) have been shown to have neuroprotective effects in a variety of *in vitro* and *in vivo* disease models. The two nutraceuticals under investigation in this study are rosmarinic acid and carnosic acid, compounds found at substantial concentrations in the herb rosemary. Here, the ability of these compounds to attenuate damage to cultured cerebellar granule neurons (CGNs) was observed and compared. Rosmarinic acid and carnosic acid both significantly reduced cell death induced by the nitric oxide donor, sodium nitroprusside. Rosmarinic acid but not carnosic acid, notably protected neurons against glutamate-induced excitotoxicity. Finally, carnosic acid displayed a unique ability to protect CGNs from caspase-dependent, intrinsic apoptosis induced by removal of serum and depolarizing extracellular potassium (5K apoptotic condition). Carnosic acid protected CGNs from 5K-induced apoptosis through a MAPK-independent but PI3K-dependent pathway. These results demonstrate that carnosic acid and rosmarinic acid have both overlapping and distinct neuroprotective effects on a range of stressors implicated in neurodegeneration. Thus, these nutraceuticals may act in either a complementary or possibly synergistic manner to protect susceptible neuronal populations in various disease states.

Disclosures: F.I. Taram: None. **E. Ignowski:** None. **D. Linseman:** None.

Poster

767. Neurotoxicity: Neuroprotective Mechanisms

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 767.11/C89

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NRF grants from the Ministry of Education NRF-2014R1A1A2058842

Title: Zinc modulates autophagy flux via regulation of cathepsins activity and expression

Authors: *K. KIM, S. KANG, R. MEHMOOD, Y. KIM;
Sejong Univ., Seoul, Korea, Republic of

Abstract: Recent studies have suggested that intracellular free zinc regulates autophagy and autophagic cell death in cultured neurons and astrocytes. Increase of intracellular zinc by zinc ionophore, clioquinol, or neurosteroids such as allopregnanolone and progesterone activated autophagy showing the increase of LC3-II conversion and reduction of mutant huntingtin (mtHtt) aggregates. In addition, oxidative stress-induced autophagic cell death was mediated by release of intracellular zinc, which induced lysosomal membrane permeabilization (LMP) and resultant cell death. In the present study, we examined whether an increase of extracellular zinc activates autophagy flux and which molecules are involved in zinc-mediated autophagy activation. First, we found that p62 protein levels were attenuated by zinc, suggesting the increase of autophagy flux. Furthermore, blockade of autophagy flux by chloroquine or NH4Cl was also reduced by zinc. Accumulation of autophagic vesicles and p62 proteins by chloroquine was significantly diminished by zinc. Since we saw that impairment of autophagy flux in neurodegenerative diseases is related to the reduction of cathepsin B activity, we next examined whether cathepsin activity or expression may be modulated by zinc. One hour later after zinc treatment at sublethal dose, cathepsin B activity was noticeably increased in cortical neuronal cultures. In addition, mRNA and protein levels of cathepsin B, cathepsin L, and cathepsin D were also increased from 6 hr after zinc treatment. Consistent with this, mtHtt aggregates in GFP-mtHttQ74-transfected HEK cells were substantially decreased by zinc treatment. Thus, the modulation of free zinc has a potential as therapeutics for neurodegenerative disease in which abnormal protein aggregates are involved.

Disclosures: **K. Kim:** None. **S. Kang:** None. **R. Mehmood:** None. **Y. Kim:** None.

Poster

767. Neurotoxicity: Neuroprotective Mechanisms

Location: Hall A

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Program#/Poster#: 767.12/C90

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: Grant from Arabian Gulf University for research fund

Title: The protective role of erythropoietin on the histological changes in ca1 region of the hippocampus of diabetic mice

Authors: *M. A. OTHMAN[1,3], E. K. RAJAB[4], A. H. AL-ANSARI[2];
[2]Physiol., [1]Arabian Gulf Univ. Col. of Med., Manama, Bahrain; [3]Histology, Assiut Univ. Fac. of Med., Assiut, Egypt; [4]Physiotherapy, Ahlia Univ. Col. of Med. and Hlth. Sci., Manama, Bahrain

Abstract: Background: Diabetes mellitus is one of the most common metabolic disorders in humans. It is highly involved in some neurological deficits, including the CNS. This is in the form of cognitive and memory impairments. These changes could be associated with degenerative changes in the hippocampus. Finding alternative treatment for diabetic complications is a challenge for clinical neurology nowadays. Erythropoietin (EPO) is a hormone secreted mainly by the kidney and it classically stimulates erythrogenesis. A neuroprotective role for EPO has been reported in some CNS injuries like stroke and spinal cord injury. This effect is supposed to result partially from its enhancement of neurogenesis and prevention of cell death. The aim of this study was to determine whether EPO can ameliorate the degenerative effects of diabetes-induced histological changes of the CA1 region of the hippocampus. Materials and Methods: Eighteen male BALB/c mice (7 weeks old) were divided into three groups of 6 animals each. Group I: the control group, injected sodium citrate intraperitoneally (IP) every other day for 6 weeks. Group II: injected streptozotocin in sodium citrate (IP) for 5 days. Group III: injected streptozotocin in sodium citrate (IP) for 5 days and after 6 weeks injected EPO (IP) every other day for 6 weeks. After sacrificing the animals, the brain was obtained from the three assigned groups and processed for light microscopic evaluation of CA1 region of the hippocampus. Results: In the diabetic mice, the CA1 region of the hippocampus appeared to have some degenerative changes. These changes were in the form of cell loss and shrinkage and darkening of the nuclei of other cells. After administration of EPO there was improvement in the neurogenesis and also in the nuclear shape of the cells of the CA1 region of the hippocampus of diabetic mice. Conclusion: Diabetes resulted in histological degenerative changes in the CA1 region of the hippocampus. These changes were ameliorated by the administration of EPO which may be useful in the treatment of diabetic neuropathy.

Disclosures: M.A. Othman: None. **E.K. Rajab:** None. **A.H. Al-Ansari:** None.

Poster

767. Neurotoxicity: Neuroprotective Mechanisms

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 767.13/C91

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: CalciGenix

Title: Oral administration of AQ is neuroprotective in an acute slice model of oxygen-glucose deprivation

Authors: *E. L. ADAMS, V. L. EHLERS, N. B. FETTINGER, S. C. MICHELS, J. R. MOYER, Jr;
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Abstract: Stroke is a leading cause of death among adults over the age of 65 in the United States (Go et al., 2013). Due to the lack of treatments for this disease, a need for novel neurotherapeutics prevails. A hallmark of ischemic stroke is excessive calcium (Ca2+) influx into cells, triggering cytotoxic signaling cascades leading up to and including cell death (Choi et al., 2009). By binding excess Ca2+, it may be possible to reduce neuronal cell death and improve outcomes for stroke victims. Our lab has recently shown that an intrahippocampal infusion of the Ca2+-binding protein (CaBP) apoaequorin (AQ) is neuroprotective in an *in vitro* model of ischemia called oxygen-glucose deprivation (OGD; Detert et al., 2013). Because it was observed that cytokine mRNA expression was altered following AQ infusion, a neuroimmunomodulatory mechanism may contribute to the observed neuroprotection. The current study tests the hypothesis that oral administration of AQ is neuroprotective in our *in vitro* OGD model. In order to study the effects of daily administration of AQ on neuroprotection, rats in the experimental groups began to receive 48 mg/kg AQ added to their peanut butter (PB) either 1h, 1d, 2d, or 7d prior to carrying out the *in vitro* OGD experiments. All control rats were fed ½ tsp PB for 9 days. On the last day, brains were extracted and hemisected. One hemisphere was subjected to *in vitro* OGD, while the other hemisphere was micro-dissected and dorsal hippocampus processed for protein analyses (e.g., AQ, IL-10, TNF-α, and β-actin). It was found that oral administration of AQ was significantly neuroprotective following 1 hour, 1 day, or 2 days of oral administration ($p < .05$). A neuroprotective effect was observed following 7 days of oral administration but this effect was not statistically significant, suggesting the need for more experiments at longer time points. These neuroprotective effects were paralleled by a significant 25% increase in IL-10 protein expression at the 1h time point ($p < .05$). TNF-α protein expression gradually increased over time from 1h until 7 days, at which point a significant 64% increase in TNF-α protein was observed as compared to control animals ($p < .05$). These results suggest that neuroprotection by oral administration of AQ may be in part due to modulation of cytokine expression.

Disclosures: E.L. Adams: A. Employment/Salary (full or part-time):; Quincy Bioscience. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or

consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; CalciGenix. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); CalciGenix. **V.L. Ehlers:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; CalciGenix. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); CalciGenix. **N.B. Fettinger:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; CalciGenix. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); CalciGenix. **S.C. Michels:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; CalciGenix. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); CalciGenix. **J.R. Moyer:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; CalciGenix. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); CalciGenix.

Poster

767. Neurotoxicity: Neuroprotective Mechanisms

Location: Hall A

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant P20MD006988

Title: Docosahexanoic acid protection under lipotoxicity: role of pi3k/akt pathway

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Abstract: Lipotoxicity induced by an overload of saturated fatty acids results in cells and tissue damage and can play an important role during traumatic and hypoxia/ischemic injuries in nerve tissues. In contrast, docosahexaenoic acid (DHA), an n-3 polyunsaturated fatty acids, has been shown to have neuroprotective roles. We have shown that Palmitic Acid, a saturated fatty acid, induces apoptotic cells death through an increase of oxidative stress, ER stress and mitochondria

dysfunction in Schwann cells as well as in neuronal cells. In this study, we investigated the protective effect of DHA against PA-induced lipotoxicity (PA-LTx) in primary Schwann cells (pSC) and the involvement of the PI3K/AKT pathway. Primary Schwann cells were cultured in EG (5.5 mM glucose) and HG (17 mM glucose) environments for 5 days and followed by treatment with PA:BSA (300 μM: 150 μM) in the presence or absence of DHA (50-200 μM) for up to 48 hrs. Cell viability was determined by crystal violet staining, nuclear morphology was examined using Hoechst staining and protein expressions were measured by Western blots. Overload of PA decreased cell viability and induced apoptosis as demonstrated by the increased number of chromatin condensations in pSC under euglycemic (EG) and high glucose (HG) conditions. Co-treatment of DHA (50 μM) with PA restored the cell viability and eliminated the chromatin condensation in both EG and HG conditions. Next, post-treatment experiments were performed. We found that the protective effects of DHA decreased dramatically if it was added 12 hrs after exposure to PA; however, significant protection was observed when the DHA was added within 6 hrs. Further, we found that PA decreases AKT phosphorylation in pSC in a time-dependent manner, however in the presence of DHA, the p-AKT levels were restored towards the control level. Thereafter, selected PI3K/AKT inhibitors were used to investigate the implication of the PI3K/AKT pathways in DHA protection of pSC from PA-LTx. Our data show that LY294002 and BMK120, but not Wortmannin, significantly decreased the protective effect of DHA under PA-LTx, shown by decreasing AKT phosphorylation, decreasing the cells viability and increasing the chromatin condensation in EG and HG conditions. In conclusion, our results demonstrate that DHA protects Schwann cells from PA-LTx and that the PI3K/AKT is involved in the protective effect of DHA.

Disclosures: M. Descorbeth: None. **M. De Leon:** None.

Poster

767. Neurotoxicity: Neuroprotective Mechanisms

Location: Hall A

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: John Baldwin Professorship

Neuroscience Program

Title: Vitamin-D3 upregulation of synaptic proteins, activity- dependent neuroprotective protein and bcl-xL may provide neuroprotection to cortical neurons

Authors: S. KANG[1], K. BLACKBURN[1], D. SLAWSKI[3], *J. K. MORRIS[2];
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Abstract: Vitamin-D_3 is a multi-function agent that has been well studied in bone and calcium metabolism. Deficiencies in vitamin D have been linked to neuropsychiatric and neurodegenerative disorders such as schizophrenia, Parkinson's disease, or Alzheimer's disease due to alterations in brain neurochemistry. Previously vitamin D was demonstrated to protect cortical neurons treated with anesthetic doses of the ketamine, NMDA antagonist, induced apoptotic cell death in the neonatal rat neurons. Neuroprotective effects of vitamin D may include: increased calcium binding proteins, increased neurotrophic factors such as GDNF, NGF, regulation of iNOS (nitric oxide synthase), as well as, decrease in L-type calcium channels. In order to determine the neuroprotective effects of vitamin D, we analyzed the somatosensory cortex, and cingulate cortex for an increase in neurons expressing calcium binding protein (CBP, calretinin, calbindin, or parvalbumin), in tissues exposed to vitamin-D_3, ketamine or a combination. The vitamin-D_3 (0.5 μg/kg) did not significantly increase the number of cells expressing CBP, except for a significant increase (237.71%) in calretinin-positive neurons in the cingulate cortex. Activity-dependent neuroprotective protein (ADNP), Bcl-X_L, PSD-95, and synaptophysin were all increased in the cortex in rats injected with vitamin D while, bax and bcl-2 were decreased in cortical tissue exposed to an anesthetic dose of ketamine (20 mg/kg). The increase in bax correlated with increased caspase-3 positive neurons following an anesthetic dose of ketamine. Thus vitamin-D_3 may enhance neuron cell health as demonstrated through increased synaptogenesis (PSD-95 and synaptophysin), alteration in pro-apoptotic factor, bax, and increased production of anti-apoptotic factor, bcl-x_L.

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Poster

767. Neurotoxicity: Neuroprotective Mechanisms

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: UDG-PTC 1039 para AERM

CONACYT 149059 y 180268 para AERM

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Title: Gene expression is modulated by pleiotrophin absence in the hippocampus of knockout mice

Authors: *A. E. ROJAS-MAYORQUIN[1], C. GONZÁLEZ-CASTILLO[2], C. GUZMÁN-BRAMBILA[3], M. PALLÀS[4], D. ORTUÑO-SAHAGÚN[2];
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Abstract: Pleiotrophin (PTN) is a secreted growth factor associated with the extracellular matrix. It is expressed in several tissues, where its signals are generally related with cell proliferation, growth, and differentiation by acting through different receptors. In Central Nervous System (CNS), PTN exerts post-developmental neurotrophic and -protective effects, and additionally has been involved in neurodegenerative diseases and neural disorders. Its expression increases after cerebral lesion or damage, and in some degenerative diseases such as in patients with Parkinson disease. Specifically in the hippocampus, PTN-deficient mice exhibit a lowered threshold for induction of LTP, which is attenuated in mice overexpressing PTN, involving PTN functioning in learning and memory and exerting post-developmental neurotrophic and -protective effects. However, molecular evidence is scarce regarding the complex signaling system involved in PTN modulatory activity. Thus, to address this aspect, we analyzed the gene expression profile by means of microarrays of 22,000 genes in the hippocampus from mice lacking PTN (PTN-/-). Microarray analysis showed that 102 genes are differentially expressed (z-score >3.0) in PTN-null mice. For group analysis, we selected only genes that range from a median z-score over (or under) 3.0. Of these, a total of 41 identified genes (40%) are of unknown function, which indicates that PTN deficiency elicits an unmapped response. The genes known to have increased are mainly related with neuroprotection, cell differentiation and proliferation, and transcriptional regulation. Conversely, genes that diminished PTN expression are mainly related with cytoskeleton, cell cycle regulation, neural development, ion transport, and signal transduction. Eight genes that modify its expression (increasing or decreasing) in hippocampus of knockout (KO) mice also modify its expression *in vitro* after silencing PTN by siRNA. Therefore, our results indicate that absence of PTN affects the expression of genes related with neuroprotection (Mgst3 and Estrogen receptor 1) and cell differentiation (Caspase 6, Nestin, and Odz4), both *in vivo* and *in vitro*. Consequently, it leads us to propose that PTN function as a neuromodulatory peptide in the CNS. The outcome of this analysis constitutes a strong starting point in the identification and study of groups of genes involved in compensatory mechanisms activated by the absence of PTN, providing a model for analyzing some aspects of neurodegenerative diseases.

Disclosures: A.E. Rojas-Mayorquin: None. **C. González-Castillo:** None. **C. Guzmán-Brambila:** None. **M. Pallàs:** None. **D. Ortuño-Sahagún:** None.

Poster

767. Neurotoxicity: Neuroprotective Mechanisms

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant P20 GM109098

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Title: Geissoschizine methyl ether, an alkaloid from the Uncaria hook, protects oxidative stress-mediated cytotoxicity in neurons

Authors: *J. SUN[1], D. YUAN[2], X. REN[1], W. QI[2], J. W. SIMPKINS[1];
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Abstract: The brain exhibits a higher demand for oxygen and glucose than any other tissue of human body. During ATP production, reactive oxygen species (ROS) are unavoidably generated. The accumulation of ROS leads to dysfunction of various subcellular organelles. Oxidative stress has been linked to the development of many neurodegenerative conditions. Glutamate-induced oxidative stress is a known cause of pathological cell death in neurons. This process is initiated by the depletion of antioxidant glutathione (GSH) synthesis by blocking cysteine uptake, and is followed by an accumulation of ROS. Buthionine sulfoximine (BSO), an inhibitor of gamma-glutamylcysteine synthetase, also blocks GSH synthesis by inhibiting the rate-limiting synthetic step. Geissoschizine methyl ether (GM) is an indole alkaloid found in Uncaria Hook, and has been identified as the active component responsible for the anti-aggressive effects of the Uncaria Hook-containing traditional Japanese medicine, Yokukansan. In this study, we examined the protective effect of GM on oxidative stress-mediated cytotoxicity. GM prevented glutamate-induced cytotoxicity in HT-22 neuronal cell line even with a 9 hr treatment delay. GM blocked glutamate-induced intracellular ROS and mitochondrial superoxide accumulation without preventing GSH depletion. We found that GM profoundly deceased mitochondrial respiration and increased glycolysis. We suspect that inhibition of mitochondrial respiration by GM may contribute to preventing glutamate-induced ROS accumulation. Moreover, GM protected cells from both glutamate and BSO toxicity in the immature rat primary cortical neurons. This study is the first to demonstrate the protective effect of GM on oxidative stress-mediated cytotoxicity in both transformed neuronal cell line and primary cortical neurons. These significant data may

provide a clinically-relevant argument for using GM against acute neuron-compromising conditions.

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Poster

767. Neurotoxicity: Neuroprotective Mechanisms

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: IN204213 PAPPIT UNAM

Title: B-hydroxybutyrate protects against glucose deprivation-induced neuronal death by the stimulation of the autophagic flux

Authors: ***L. CAMBEROS LUNA**, C. GERÓNIMO-OLVERA, T. MONTIEL, R. RINCÓN-HEREDIA, L. MASSIEU;
Neuropatología Molecular. Lab. AL-302, Inst. De Fisiología Celular, UNAM, Ciudad de México, Mexico

Abstract: Ketone Bodies (KB), acetoacetate (AcAc) and b-hydroxybutyrate (BHB) are formed as an end product of lipid catabolism in the liver and can be used as metabolic fuel in certain conditions such as prolonged fasting, the ketogenic diet, breastfeeding and severe hypoglycemia. Increasing evidence supports the neuroprotective action of KB in models of neurodegenerative disorders, epilepsy, hypoglycemia, excitotoxicity and ischemia. The mechanisms of protection of KB are not completely understood but several studies have suggested that the improvement of energy metabolism is one of the major factors involved in KB protective action. In the present study we have investigated whether the D isomer of BHB (D-BHB) prevents neuronal death induced by glucose deprivation (GD) in cortical neurons, through the modulation of autophagy. Autophagy is a lysosomal-dependent degradation process activated during nutritional stress, that digest damaged proteins and organelles providing energy for cell survival. Primary cultures of cortical neurons obtained from rat E17 embryos, were exposed at 8 DIV to GD followed by different times of GR either with or without D-BHB. We used viability assays (MTT reduction and lactic dehydrogenase release to culture media) western blot, immunocytochemistry and confocal microscopy, to investigate the effect of D-BHB on autophagy and neuronal death. Immunoblot results indicate that during GD the levels of the autophagic markers p62 and LC3-II

(the lipidated form of the microtubule associated protein light chain 3) increase, as well as the number of autophagic vesicles, according to LC3 immunocytochemistry and confocal microscopy for the the autophagosome marker Cyto-ID. During glucose reperfusion (GR) autophagosomes and the levels of LC3-II and p62 decrease, suggesting autophagic degradation. Cultures exposed to GD in the presence of D-BHB show a lower increase in LC3-II and p62 during GD and a faster decrease in autophagic markers during GR. Results suggest that D-BHB stimulates the autophagic flux improving neuronal survival. This study was supported by IN204213 PAPPIT grant to LM.

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Poster

767. Neurotoxicity: Neuroprotective Mechanisms

Location: Hall A

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: ART/PG2009/5

ARUK-ESG 2013-8

Title: PGC-1α gene delivery in the brain reduces Aβ generation, prevents neuronal loss and improves spatial and reference memory in a mouse model of Alzheimer’s disease

Authors: *L. KATSOURI, Y. M. LIM, A. M. BIRCH, N. MIRZAEI, N. D. MAZARAKIS, M. SASTRE;
Imperial Col., London, United Kingdom

Abstract: The PPARγ co-activator 1alpha (PGC-1α) is a transcriptional regulator that is involved in mitochondrial biogenesis and in the control of genes regulating oxidative stress and inflammation. We have found that the brains of Alzheimer's disease (AD) patients have decreased PGC-1α compared to healthy controls and that overexpression of PGC-1α increases the neurotrophic soluble APPα and reduces Aβ generation, thus implying that PGC-1α overexpression could be protective against AD. The aim of this study was to investigate whether PGC-1α can be used as a therapeutic target for AD by overexpressing it in the neurons of a transgenic mouse model of AD. For this purpose, we used an HIV-based lentiviral vector system and we subcloned the human PGC-1α cDNA in the lentiviral transfer genome downstream of the

human cytomegalovirus immediate early gene enhancer promoter (CMV). The vectors were pseudotyped with the rabies virus glycoprotein (RVG). Lentiviral vectors expressing either eGFP or PGC-1α were delivered by stereotaxic injection bilaterally in the frontal cortex and the hippocampus of eight month old female wild-type and AD transgenic mice (APP23). At this age there is no plaque formation in the APP23 mice, resembling a preclinical AD stage. Behavioral performances on the object location and object recognition tasks at four months post-surgery showed that the APP23 mice that received the PGC-1α vector have improved spatial and reference memory compared to the control group. Protein and immunohistochemical analysis revealed a significant decrease in total plaque numbers and Aβ load in animals injected with PGC-1α as well as a reduction in proinflammatory cytokines. Most strikingly, PGC-1α overexpression in the brain prevented neuronal loss in the cortex and the CA3 area of the hippocampus. These effects coincided with increased synaptophysin and PSD-95 expression and enhanced brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) mRNA levels, supporting a neuroprotective role for PGC-1α in this AD mouse model. Our data suggest that PGC-1α gene therapy could be a strong therapeutic candidate in AD.

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Poster

767. Neurotoxicity: Neuroprotective Mechanisms

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: 1| 01BX000819

Title: The primary function of the hypocretinergic system is to promote survival in health and disease states

Authors: *M. H. CHASE[1,2,3], M. XI[1,2], S. FUNG[1,2], J. ZHANG[1], S. SAMPOGNA[1]; [1]Websciences Intl., Los Angeles, CA; [2]VA Greater Los Angeles Healthcare Syst., Los Angeles, CA; [3]UCLA Sch. of Med., Los Angeles, CA

Abstract: Wakefulness and motor activity are produced by the Reticular Activating System (RAS) in the brainstem. Wakefulness and motor activity are also promoted by the hypocretinergic system (HS) in the lateral hypothalamus. Is there a difference in these waking and motor behaviors? The answer is: Yes. Whereas the RAS responds to most alerting stimuli

and induces a generalized increase in motor activity, only survival-related stimuli activate the HS, which produces wakefulness, specific survival-related motor behaviors and a variety of related directives. Accordingly, we propose that the primary function of the HS is to promote survival-related behaviors and related responses that include cellular and subcellular processes. We have previously reported that hypocretinergic neurons discharge selectively during the pursuit of a food reward or during the exploration of a novel environment. Conversely, using antisense to disrupt hypocretinergic actions, we determined that there is a dramatic decrease in exploratory behaviors and a lack of reactivity to external threats. We have also found that the HS control extends to a variety of peripheral functions involving the pancreas, the adrenal gland and other organs. The maintenance of cellular and subcellular activities is also critical to survival. In this regard, we found that hypocretin suppresses apnea-induced hyperexcitability and subsequent neurotoxic changes in hippocampal neurons. Consistent with these electrophysiological findings, our morphological analyses reveal that hypocretin significantly reduces apnea-induced apoptosis (neurodegeneration). We also postulate that the survival directives of the HS include the amelioration of disease processes. To examine this hypothesis, hypocretin and vehicle solution were administered intraperitoneally (daily for 14 days) to control mice without cancer and mice with colon cancer. The animals were subsequently sacrificed and the colon in all groups of animals was examined with H&E staining. Remarkably, cancer mice that were treated with hypocretin exhibited normal colon epithelia. Hyperplasic/neoplasiac changes continued to be present in the epithelia of the colon of cancer mice treated with vehicle solution. No changes were found in the colon of control mice treated with hypocretin and vehicle solution. These data support our hypothesis that the primary function of the HS is to promote all aspects of the organism's survival, extending from behavioral to cellular and subcellular activities. Moreover, we propose that these directives of the HS are promulgated during health as well as disease states.

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Poster

767. Neurotoxicity: Neuroprotective Mechanisms

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Title: Proteinase-activated receptor 2 (PAR2) and neuroprotection: Characterising novel activators in a CNS preparation

Authors: *S. MOUDIO;
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Abstract: Proteinase-activated receptor 2 (PAR2), a subtype of GPCRs linked with inflammation, has recently received increasing interest due to their potential neuroprotective role in CNS diseases. Investigating the role and properties of PAR2 in CNS was previously made difficult by the limited selectivity and potency of PAR2 activators. Recently however, novel PAR2 activators with high potency and good stability have been developed allowing further investigation. Here, we characterise them for the first time in a CNS preparation. PAR2 activation has previously been shown to increase intracellular Ca^{2+} levels in both neurons and astrocytes. In the present study, we have utilised the recently developed PAR2 activators, GB110 and AC264613 as well as a proposed PAR2 antagonist, GB88 to determine their effects on intracellular Ca^{2+} levels in rat primary hippocampal cultures (12-15 DIV). In agreement with previous studies, our results demonstrate that activating PAR2 causes an increase of in intracellular Ca^{2+} levels in both neurons and astrocytes with GB110 (100μM) and AC264613 (100μM) resulting in an increase of 139 ±5% (n=35, $P<0.05$) and 77 ±3% (n=22, $P<0.05$) respectively in neurons and of 187 ±6% (n=26, $P<0.05$) and 92 ±3% (n=31, $P<0.05$) in astrocytes. In contrast, GB88 (100μM) produced a small but significant decrease in intracellular Ca^{2+} levels in both neurons 10 ±2% (n=37, $P<0.05$) and astrocytes 17 ±2% (n=33, $P<0.05$). To investigate further the underlying mechanisms behind PAR2 activation, we performed internalisation studies using PAR2-YFP transfected tSA201 cells. PAR2 internalisation was evident following exposure to all PAR2 compounds that elevated intracellular Ca^{2+} levels, including GB88 suggesting that it may actually be a biased agonist. Moreover, to assess the specificity of these PAR2 activators, we applied them to PAR1 and PAR4 transfected tSA201 cells with no internalisation being observed. Building on our previous work revealing the neuroprotective effects of PAR2 activation, we are currently testing the hypothesis that these novel PAR2 activators are neuroprotective against the *in vitro* kainate induced model of neurotoxicity in hippocampal organotypic slices cultures. Determining the potential of PAR2 as a novel therapeutic for CNS disorders may provide new options for a large range of CNS diseases.

Disclosures: S. Moudio: None.

Poster

767. Neurotoxicity: Neuroprotective Mechanisms

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 767.22/D4

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: National Natural Science Foundation of China (81401043)

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Title: Spermidine prevents staurosporine-induced neuronal cell death by inhibiting caspase-mediated Beclin 1 cleavage

Authors: *Y. YANG[1], Y. ZHANG[1], S. CHEN[2], X. LIN[1], Y. SONG[1], C. LI[1];
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Abstract: Spermidine is a natural polyamine that opposes age-related beneficial effects. However, the mechanism of spermidine-mediated neuroprotection remains unclear. In this study, we determined the effects of spermidine against staurosporine (STS)-induced PC12 cell death. Our findings demonstrated that STS resulted in cell apoptosis which could be efficiently reversed by the addition of caspase inhibitor z-VAD-fmk. STS-triggered cell apoptosis was accompanied with enhanced autophagic activity and Beclin 1 (the key autophagy modulator) cleavage. Administration of spermidine alone or in combination with z-VAD-fmk relieved STS-induced cell injury. Moreover, STS caused partial nuclear translocation of Beclin 1, which could be suppressed by spermidine. PC12 cells were overexpressed with full length, N- or C-terminal fragment of Beclin 1. Neither full length nor N-terminal Beclin 1 fragment affected cell survival. However, overexpression of C-terminal Beclin 1 fragment led to cell shrink, neurite loss, and caspase 3 activation in cells. Additionally, PC12 cells were transfected with Beclin 1 wide type (WT), or plasmids with site mutations (D121/124A, D146/149A, or D121/124/146/149A). D146/149A but not D121/124A resisted to STS-induced nuclear translocation of Beclin 1 and cell damage. Our results suggest that STS-induced caspase 3 activation and subsequent Beclin 1 cleavage, possibly at the site of D146/149, in PC12 cells. Addition of spermidine protected against cell injury by suppressing caspase-mediated Beclin 1 cleavage. These findings provide valuable insights for clarifying the crosstalk between autophagy and apoptosis within Beclin 1 interactome during neuronal cell death, and also provide basic evidences for understanding the mechanism of spermidine-mediated neuroprotection.

Disclosures: **Y. Yang:** None. **Y. Zhang:** None. **S. Chen:** None. **X. Lin:** None. **Y. Song:** None. **C. Li:** None.

Poster

767. Neurotoxicity: Neuroprotective Mechanisms

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 767.23/D5

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Title: Investigating the disease-modifying efficacy of voluntary exercise in experimental Multiple Sclerosis

Authors: A. GENTILE[1,2], S. BULLITTA[1], D. FRESEGNA[1,2], A. MUSELLA[1], F. DE VITO[1,2], *G. GRASSELLI[3], G. MANDOLESI[1], D. CENTONZE[2,4];
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Abstract: Multiple Sclerosis (MS) is a neuroinflammatory disease and the most common cause of disability among young adults. Current therapeutic approaches are based on immunomodulants or immunosuppressants, able to provide functional recovery. Both clinical and preclinical data strongly suggest the beneficial effect of rehabilitative therapies for progressive multiple sclerosis (MS) patients, but the mechanisms involved are still poorly understood. In recent years a link between inflammation and synaptic alteration in several brain areas, like the cerebellum, has been highlighted in the experimental autoimmune encephalomyelitis (EAE), animal model of MS. In particular, we have recently shown that the pro-inflammatory cytokine interleukin 1-beta (IL1-beta), released by T-lymphocytes, has a crucial role in triggering cerebellar synaptic defects. Interestingly, symptoms linked to cerebellar dysfunction in MS seem to be responsive to motor training. We asked whether exercise could attenuate peripheral and central inflammatory reaction, thereby leading to amelioration of cerebellar pathology in the EAE model. To this aim, MOG35-55 EAE was induced in 8-week female C57BL6/N mice: the day of the immunization mice were randomly assigned to standard and wheel-equipped cages (voluntary exercise protocol). Daily clinical score analysis revealed significant reduction in disease-related disability in exercised-EAE mice. Also, grip strength test showed increased neuromuscular function in exercised-EAE mice. At the peak of the acute phase (21 days post immunization-21 dpi), mice were sacrificed and cerebella and spleens were isolated for biochemical analysis. First, we measured the levels of IL1-beta released by peripheral T-lymphocytes isolated from the spleens of exercised and non-exercised EAE mice: we found that exercise reduced consistently the amount of IL1-beta released by EAE-specific T-lymphocytes. As a measure of central inflammation we checked astrogliosis, by western blot analysis for glial fibrillary acidic protein (GFAP) in cerebellar extracts of both experimental

groups: GFAP protein levels were significantly reduced in exercised-EAE mice. Overall these data, although preliminary, provide evidence for an anti-inflammatory effect of voluntary exercise with a potential impact on cerebellar alteration of neurotransmission, corroborating the hypothesis that physical exercise is able to interfere with MS/EAE pathological mechanisms.

Disclosures: **A. Gentile:** None. **S. Bullitta:** None. **D. Fresegna:** None. **A. Musella:** None. **F. De Vito:** None. **G. Grasselli:** None. **G. Mandolesi:** None. **D. Centonze:** None.

Poster

767. Neurotoxicity: Neuroprotective Mechanisms

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant RO3-NS074286

Theresa Pantnode Santmann Foundation Award

Title: Serotonin as a scavenger of hypochlorous acid in the brain

Authors: ***T. M. JEITNER**[1], M. KALOGIANNIS[2], E. J. DELIKATNY[3];
[1]New York Med. Col., Valhalla, NY; [2]Winthrop Univ. Hosp., Mineola, NY; [3]Radiology, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Hypochlorous acid (HOCl) is a powerful two-electron oxidant produced in the brains of Alzheimer Disease, Parkinson Disease or cerebral stroke patients. At present there are no effective antioxidant therapies for the treatment of neurodegenerative diseases. HOCl reacts with neurotransmitters to produce products of varying toxicity (Jeitner et al. (2015) BBA 1852: 937). The aim of these studies was to assess the scavenging of HOCl by serotonin. HOCl altered the UV-visible and 1H-NMR spectra of serotonin indicative of chlorination of the nitrogen atoms. These reactions led to the polymerization and aggregation of chlorinated serotonin. HOCl scavenging was assessed by monitoring the oxidation of 2-thio-5-nitrobenzoate by HOCl. Serotonin prevented this reaction. Each molecule of serotonin scavenged more than one molecule of HOCl. Indeed, scavenging was more effective at ratios of HOCl to serotonin ≥ 1:1. This behavior was also exhibited in the protection of cells from the toxicity of HOCl by serotonin. Cellular alpha-ketoglutarate dehydrogenase complex activity was similarly protected from HOCl-mediated inactivation by serotonin. HOCl and serotonin are readily increased in the brain by the administration of LPS and selective serotonin-reuptake inhibitors, respectively.

Administration of selective serotonin-reuptake inhibitors to LPS-treated mice prevented the chlorination of cerebral proteins by HOCl, as well as sickness behavior induced by LPS. These demonstrations suggest serotonin may an effective scavenger of HOCl in the diseased brain.

Disclosures: T.M. Jeitner: None. **M. Kalogiannis:** None. **E.J. Delikatny:** None.

Poster

767. Neurotoxicity: Neuroprotective Mechanisms

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Program#/Poster#: 767.25/D7

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: CNPq

IPA

FAPERGS

CAPES

Title: Effects of treatment with white grape juice on inflammatory cytokines on rats exposed to carbon tetrachloride

Authors: *C. S. FUNCHAL[1], A. ABUJAMRA[2], F. MACHADO[2], M. WOHLENBERG[2], N. MEDEIROS[2], V. ELSNER[2], C. DANI[2];
[1]Ctr. Universitário Metodista, Porto Alegre, Brazil; [2]Ctr. Universitário Metodista -IPA, Porto Alegre, Brazil

Abstract: Grape juice is considered a source of phenolic compounds which act as antioxidating agents and, therefore, are beneficial to those who consume them. The anti-inflammatory potential of white grape juice, however, has not yet been evaluated. The purpose of this work was to evaluate the effect of organic and conventional white grape juice on the inflammatory cytokines interleukin 1 beta (IL-1β) and interleukin 6 (IL-6) in the cerebral cortex, liver, and serum of adult rats submitted to an experimental model of hepatic encephalopathy. Forty male Wistar rats aged 90 days were treated daily, once a day, orally by gavage, with organic or conventional white grape juice during 14 days, at a dose of 7 μL/g of body weight. On the 15th day, rats received a single dose (3.0mL/Kg of body weight) of carbon tetrachloride (CCl4). Four hours later, rats were euthanized and dissected for organ harvesting and blood collection. Blood serum and cellular lisates of cerebral cortex and liver were utilized for a sandwich ELISA with

antibodies against IL-1β and IL-6. Multivariate analysis of variance (MANOVA) followed by the Tukey HSD post-hoc test was utilized to obtain the results presented herein. Rats exposed to CCl4 demonstrated a significantly higher concentration of IL-1β and IL-6 in blood serum and tissues when compared to control rats. Rats which received organic white grape juice for two weeks previously to CCl4 exposure demonstrated blood serum and tissue concentrations of IL-1β and IL-6 similar to control rats, preventing an increase in IL-1β and IL-6. These results suggest that white grape juice prevented the proinflammatory effects of CCl4, and therefore should be investigated more extensively as a potential anti-inflammatory therapy for various diseases.

Disclosures: C.S. Funchal: None. **A. Abujamra:** None. **F. Machado:** None. **M. Wohlenberg:** None. **N. Medeiros:** None. **V. Elsner:** None. **C. Dani:** None.

Poster

768. Cellular Mechanisms of Degeneration and Inflammation in Models of Neurodegenerative Disease

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 768.01/D8

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R01 AG046170

Title: Multiscale network modeling of myelination dysregulation in Alzheimer’s disease

Authors: *A. T. MCKENZIE[1], M. WANG[1], J. ZHU[1], K. A. NAVE[2], B. POPKO[3], B. ZHANG[1], P. CASACCIA[1];
[1]Icahn Sch. of Med. At Mt Sinai, New York, NY; [2]Max Planck Inst., Gottingen, Germany; [3]Univ. of Chicago, Chicago, IL

Abstract: Alzheimer’s disease (AD) is a neurodegenerative disease causing a progressive dementia that affects approximately 1/6th of people in the US age 75 and above. Despite intensive research in the past decades, the underlying mechanisms of AD remain elusive. Genetic, histological, and brain imaging data suggest that oligodendrocytes and myelination may play important roles in AD pathology. Despite intriguing reports and enticing preliminary data, a molecular-level characterization of modifications in oligodendrocytes and myelination in AD has not yet been established. Our previous study showed that myelination/oligodendrocyte-enriched gene networks were enriched for AD GWAS hits and contained the amyloid-production related genes PSEN1 and BACE1. Towards this end, we have analyzed public human brain

transcriptome data at different stages of cognitive decline using a network-based approach to interrogate the molecular structure of AD pathogenesis. Our results suggest that the myelination networks are highly dysregulated at the early stage of AD. We systematically validated five key drivers of the myelination networks using several mouse models in which these key drivers were perturbed. Using RNA-seq of samples isolated from the same brain regions that were analyzed in the human cohort, we were able to confirm in mice the key findings from the human analysis. Our results provide novel insights into the mechanisms underlying the dysregulation of oligodendrocytes and myelin in AD, and unlock potential novel molecular targets for AD in oligodendrocytes.

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Poster

768. Cellular Mechanisms of Degeneration and Inflammation in Models of Neurodegenerative Disease

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 768.02/D9

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: James Madison University Biology Department

Title: Modulation of nitric oxide synthase I transcription by tau and alpha-synuclein

Authors: ***T. K. RIFE**, D. M. JALIL, A. L. DEAL, T. A. WEAVER, M. M. HUTH;
Biol., James Madison Univ., Harrisonburg, VA

Abstract: Transcriptional regulation of Nitric Oxide Synthase I (NOS1), an enzyme which produces nitric oxide (NO), plays a role in sleep regulation, one's ability to learn and remember, synaptic plasticity, and brain development. Additionally, excessive expression of NOS1 plays a role in many neurodegenerative diseases like Parkinson's Disease, Alzheimer's Disease, and stroke. Hence, it is vitally important to understand how NOS1 is transcriptionally regulated. NOS1 has twelve different first exons that are each controlled by a unique promoter (1a - 1l). The 1f promoter has a dinucleotide polymorphism ($(TG)_nTA(TG)_n$) located upstream of the TATA box. Genotyping shows that shorter dinucleotide polymorphisms are associated with Alzheimer's and Parkinson's Disease and that shorter repeats have decreased transcriptional expression compared to larger repeats. Purine-pyrimadine dinucleotide repeats have been shown to form alternative DNA structures like Z-DNA. Moreover, tau and alpha-synuclein, proteins

that are misregulated in Alzheimer's and Parkinson's Disease respectively, have been shown to bind to and stabilize alternative DNA structures. Therefore, we hypothesize that tau and alpha-synuclein might be involved in regulating transcription of the 1f promoter by interacting with its repeat. Human Sk-n-Mc neuroblastoma cells, which normally express high amounts of tau and low amounts of alpha-synuclein were used to test this hypothesis. A tau siRNA was utilized to knock down tau protein in the cells. Alpha-synuclein expression was increased in the cells by transfecting them with an alpha-synuclein expression plasmid. Reporter genes directed by NOS1 1f promoter regions with and without the dinucleotide polymorphism were transfected into the cells along with the tau siRNA, alpha-synuclein expression plasmid or appropriate controls. Reporter genes containing short polymorphisms were increased two-fold following tau knockdown but no change in activity was observed in constructs that did not contain the dinucleotide polymorphism. Alpha-synuclein over-expression caused a two-fold decrease in reporter gene expression when a short dinucleotide repeat was present. These findings suggest that tau and alpha-synuclein may modulate NOS1 expression through interaction with a dinucleotide polymorphism associated with disease development. Preliminary data also suggest that tau and alpha-synuclein can affect the longer repeats differently than shorter repeats. Further studies are being done to understand the nature of tau and alpha-synuclein's effects on NOS1's 1f promoter.

Disclosures: T.K. Rife: None. **D.M. Jalil:** None. **A.L. Deal:** None. **T.A. Weaver:** None. **M.M. Huth:** None.

Poster

768. Cellular Mechanisms of Degeneration and Inflammation in Models of Neurodegenerative Disease

Location: Hall A

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Program#/Poster#: 768.03/D10

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: ADA #7-12-BS-021

Title: Role of HMGB1 inhibitor Glycyrrhizin in diabetic complications

Authors: *M. CHATTOPADHYAY, M. GONZALEZ, K. PENNINGTON, S. NARGIS, V. THAKUR;
Ctr. of Excellence in Diabetes and Obesity, Texas Tech. Univ. Hlth. Sci. Ctr., El Paso, TX

Abstract: The increases in number of diabetic patients have become an epidemic worldwide which greatly affects the quality of life of the patients. Diabetic neuropathy and diabetic nephropathy are very common complications among all diabetes patients. Recent evidence suggests that the inflammatory pathway plays a crucial role in the development of these complications. Unfortunately, available medical treatment is relatively ineffective due to side its effects. We have investigated the role of a number of neuropeptides and inflammatory mediators in the peripheral nervous system and in the diabetic kidney. High mobility group box 1 (HMGB1) protein is a novel biomarker of inflammation and we have recently shown that HMGB1 is up-regulated in the peripheral nervous system and kidney. This study is designed to investigate whether blocking HMGB1 by natural inhibitor, Glycyrrhizin, can reduce the progression of the development of one or both these complications. We have also demonstrated that interruption of inflammation would ameliorate the expression of certain neuropeptides in the dorsal root ganglia and kidney of diabetic animals. Successful completion of this study may serve an effective means to alleviate inflammation that is associated with certain complications in diabetes. Zucker diabetic fatty (ZDF) rats, an established model for spontaneously diabetic rats were used for Type 2 animal model. Animals with blood glucose level ~300 mg/dl was included as diabetic. We have determined whether there is a direct association between the expression of inflammatory markers, HMGB1, TNFα and IL-1β, and release of the peptide neurotransmitters, calcitonin gene related peptide (CGRP), substance P (SP) and Pituitary adenylate cyclase-activating polypeptide (PACAP) in the peripheral nervous system and kidney of the diabetic animals, by immunohistochemistry and Western blot analysis. This study demonstrates whether HMGB1-mediated inflammation is responsible for peripheral neuropathy in diabetes and whether similar or different peptide neurotransmitters are involved in the diabetic nephropathy in Type 2 diabetic animals. Successful completion of this study may provide a more useful and efficient way to treat this debilitating problem.

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Poster

768. Cellular Mechanisms of Degeneration and Inflammation in Models of Neurodegenerative Disease

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 768.04/D11

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Title: Temperature modulates stress response of neurons to repetative low-force mechanical impacts

Authors: D. C. KLINE[1,2], C. BEST-POPESCU[1,2], *P. SENGUPTA[1,2,3];
[2]Dept. of Bioengineering, [3]Beckman Inst. for Advanced Sci. and Technol., [1]Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: Low-impact force induced concussions cause brain injury in contact sport athletes and civilians. These injuries are not treated seriously and are often ignored as "little bumps on the head". However, in recent years, increasing scientific evidence has emerged implicating recurrent, low-force mechanical impact (LFMI) -induced concussions with long-term disability and persistent damage to the central nervous system (CNS). The immediate consequences of LFMI include a cascade of subcellular events that alter the equilibrium state of the neuronal network, ultimately leading to a breakdown in neuronal communication and neurodegeneration. It would greatly help victims of LFMI if somehow this stress response of neurons could be attenuated immediately after the injury. As most physiological processes have been shown to be temperature sensitive, modulation of temperature is expected to have a significant effect on LFMI-induced injury. In fact, experimental animal research has shown that both whole-body hypothermia and selective head cooling have neuroprotective effects in a variety of CNS injury models. Alternatively, raising brain temperature by a couple of degrees above normothermia worsens outcome in a variety of injury models. In addition, therapeutic hypothermia, defined as clinically reduced deep brain structure temperature to 33-34°C, is standard of care to treat patients resuscitated after cardiac arrest, because it leads to improved neurologic outcome and decreased overall morbidity and mortality. The aim of the current study was to determine the time dependent effects of hypothermia on neuronal inflammation and network signaling in an *in vitro* repetitive LFMI neuronal injury model. For experiments, disassociated cultures of primary mouse cortical neurons were used. These neurons form networks *in vitro*. A custom-built mechanical impactor was used to deliver recurrent impacts to these networks with high precision. To ensure that a solitary impact did not create any measurable effects, a sub-threshold impact force was used for all experiments. The degree of LFMI-induced inflammation was quantified by determining interleukin-1β levels in these networks, at multiple time points and following an increasing number of impacts. The networks were treated post-impact with immediate and delayed hypothermic conditions and ensuing inflammation levels were determined. Our results demonstrate that treatment with hypothermic conditions protects neurons from injury significantly by lowering levels of inflammation. These findings have direct implications in terms of effective neuroprotective treatment design and damage prevention strategies.

Disclosures: D.C. Kline: None. **C. Best-Popescu:** A. Employment/Salary (full or part-time):; Department of Bioengineering. **P. Sengupta:** None.

Poster

768. Cellular Mechanisms of Degeneration and Inflammation in Models of Neurodegenerative Disease

Location: Hall A

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Program#/Poster#: 768.05/D12

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: P01 ES022845

T32 AG-0037

Title: Sex differences in response to traffic-related air pollution exposure: male sensitivity to obesity and depressive behavior

Authors: *N. C. WOODWARD, A. CROW, Y. ZHANG, A. SAFFARI, C. SIOUTAS, H. ALLAYEE, C. FINCH, T. MORGAN;
USC, Los Angeles, CA

Abstract: Traffic-related air pollution (TRP) has a well-documented effect on cardiovascular function and mortality (Pope et al 2004). Moreover, recent studies show effects of TRP as both an obesogen and a cause of cognitive impairment (Perera et al. 2012; Sun et al. 2009; Volk et al. 2011). Our objective is to analyze the developmental impact of nanoscale particulate matter (nPM), a subfraction of TRP, on postnatal weight gain, insulin sensitivity, and behavioral-cognitive deficits. The nPM was eluted from Teflon filters, reaerosolized, and delivered to mice utilizing a novel system, which allowed exposure from conception to adulthood (Morgan et al. 2011). The exposure schedule was 3 days a week, for 5 hours per day, at a concentration of 324 ug/m3 of nPM. C57BL/6J were exposed for the duration of gestation, and the offspring were exposed from birth until 14 weeks of age. At four weeks of age the mice were put on high fat diets (45% kcal/fat), and remained on the diet until time of euthanasia. Males exposed to nPM and fed either the regular chow (6.4% kcal/fat) or high fat diet gained more weight than controls exposed to filtered room air. Their greater weight gain was observed from 4 weeks to 9 weeks of age, when the differences stabilized. In contrast, female weight was not altered by nPM exposure or diet. Males were given an intraperitoneal glucose tolerance test at 13 weeks of age. Males on both high fat diet and nPM exposure showed impaired blood glucose regulation. In behavioral tests at 12 weeks of age, males performed worse in the Porsolt forced swim test, which measures depressive symptoms. Males exposed to nPM had decreased latency to their first period of immobility, and increased total time spent immobile, corroborating findings from a prenatal only exposure in our lab (Davis et al. 2013). Females showed no changes in forced swim. In the open field test, a measure of anxiety, females exposed to nPM had an increase in total distance traveled, while the males showed no differences. No change was detected for the novel object

recognition test or elevated plus maze for either sex. Gestation and early development are critical periods in determining lifelong health, and environmental insults during this period can have disproportionate effects. This study demonstrates the impact of TRP exposure on weight gain, and cognitive functioning. Diet induced obesity is associated with neuroinflammation, which can contribute to age related cognitive decline (Jayaraman et al. 2014).These results highlight substantial sex differences in effects, with females less responsive to nPM effects on weight and depressive symptoms.

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Poster

768. Cellular Mechanisms of Degeneration and Inflammation in Models of Neurodegenerative Disease

Location: Hall A

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Program#/Poster#: 768.06/D13

Topic: F.01. Human Cognition and Behavior

Support: NIMH R21-MH085228

Title: White matter substrates of limited visual working memory capacity in schizophrenia

Authors: ***M. LAZAR**, D. MALASPINA, O. GONEN;
New York Univ. Sch. of Med., New York, NY

Abstract: *Background: Working memory (WM), which plays an essential role in many higher-order cognitive processes, has a limited capacity of only several objects. Our previous work has shown that, in healthy adults, 59% of inter-individual variability in the visual WM capacity is explained by variations in axonal density of the white matter pathways connecting brain regions involved in WM, with another 12% explained by variations in the global diffusion properties of the extra-axonal space. The goal of this study was to evaluate the relationship between visual WM capacity and white matter microstructural properties in schizophrenia (SZ), a disorder with known WM capacity limitations. Methods: 19 healthy controls (HC) and 16 right-handed male SZ patients ages 30 to 55 years old participated in the study. Visual WM capacity was measured using the Symbol Span test from WMS-IV. The Diffusional Kurtosis Imaging (DKI) approach was employed to estimate 1)Axonal Water Fraction (f_{axon}), a metric reflective of axonal density and caliber, 2) Intra-axonal Diffusivity (D_{axon}), which describe overall organization of the intra-axonal millieu and 3) Axial (AD_{extra}) and 4) Radial (RD_{extra}) extra-axonal diffusivities, which*

reflect the size, number, and organization extracellular structures such as oligodendrocytes, astrocytes, or microglial cells. RD_{extra} may also reflect axonal packing and, thus, dysmyelination, and was found to be impaired in SZ. DKI data were acquired and employed to derive three-dimensional maps of f_{axon}, D_{axon}, $AD_{extra,}$ and RD_{extra}. Tract specific and global (whole brain) mean DKI metrics were obtained from these maps. Results: No significant relationships between white matter DKI metrics and visual WM capacity were found at the tract level in the SZ group. Multiple regression identified some similar relationships to the ones found in the HC group (with f_{axon} of left inferior longitudinal fasciculus and global AD_{extra}). However, relationships to f_{axon} of left inferior longitudinal fasciculus and right cingulum were no longer present, with other axonal density contributions detected only at the global level (through the global f_{axon}). A significant contribution was detected for the RD_{extra} of the right cingulum. The overall model explained 55% of the inter-individual variations in visual WM capacity in the SZ group. Conclusion: In schizophrenia, only some of the relationships between visual WM capacity and white matter microstructural properties found in the healthy brain are maintained with atypical microstructural features reflective of dysmyelination appearing to be involved.

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Poster

768. Cellular Mechanisms of Degeneration and Inflammation in Models of Neurodegenerative Disease

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: R21 AG-040683

R21 AG-040753

Title: Rapid oxidative and inflammatory effects of acute traffic-derived nanoscale particulate matter exposure on olfactory gateways to the brain

Authors: *H. CHENG, C. E. FINCH, T. E. MORGAN;
USC, Los Angeles, CA

Abstract: Urban traffic-derived nanoparticulate matter (nPM, <200nm) can induce oxidative stress and inflammation in the brain (Morgan et al. 2011; Davis et al. 2013). To resolve the time course of brain responses, mice were exposed to nPM for 5, 20, and 45 cumulative hours over 1-

21 days to model effects of acute exposure. Because nPM can translocate into the brain *via* the olfactory receptor neurons lining the olfactory epithelium (OE) (Oberdörster *et al.* 2004*)*, we hypothesized that the OE will show the earliest responses to nPM, followed by olfactory bulb (OB) and caudal pathways and structures. OE, OB, and cerebral cortex were analyzed by Western blot for stress-responses sensitive to oxidation and inflammation. OE showed 30% increases in 4-hydroxynonenal (4-HNE) and 3-nitrotyrosine (3-NT) by 5h of exposure, and remained elevated through the 45h of exposure, whereas OB only responded at 45h. Olfactory marker protein (OMP) was slightly decreased in the OE at 45h by 20%, but unchanged in the OB. Apoptotic responses were evaluated with cleaved caspase-3, which increased by 20% in OE only after 20 and 45 hours. Cortex did not show these changes. By immunohistochemistry, the shortest exposure of 5 hours also induced 4-HNE and 3-NT in the OE, but not OB. The astrocytic marker GFAP was unchanged in OB. Iba1 positive monocyte counts were increased by 25% in OE turbinates and the glomerular layer of OB. These novel findings show rapid responses in the OE that we hypothesize will initiate subsequent early oxidative and inflammatory cascades into the brain. **References:** Davis, D. A., et al. "Urban Air Pollutants Reduce Synaptic Function of CA1 Neurons via an NMDA/NȮ Pathway." Journal of Neurochemistry 127.4 (2013): 509-19. Morgan, T.E. *et al*. (2011). Glutamatergic neurons in rodent models respond to nanoscale particulate urban air pollutants *in vivo* and *in vitro*. Environ Health Perspect *119*, 1003-1009. Oberdörster, G., *et al.* (2004). Translocation of Inhaled Ultrafine Particles to the Brain. Inhal Toxicol. *16,* 437-445.

Disclosures: H. Cheng: None. **C.E. Finch:** None. **T.E. Morgan:** None.

Poster

768. Cellular Mechanisms of Degeneration and Inflammation in Models of Neurodegenerative Disease

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 768.08/D15

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: R21 AG-040683

R21 AG-040753

T32 AG-0037

Title: Microarray analysis of traffic-related air pollution and LPS treatment of mixed glia

Authors: *E. BACON[1], N. WOODWARD[1], M. LEVINE[2], C. SIOUTAS[1], T. MORGAN[1], C. FINCH[1];
[1]USC, Los Angeles, CA; [2]Univ. of California Los Angeles, Los Angeles, CA

Abstract: Traffic-related air pollution (TRP) is a ubiquitous environmental toxin. However, little is known about the direct interaction TRP components have with cells. Increasing epidemiological evidence demonstrates TRP's role in autism and other developmental disorders (Perera et al 2012; Volk et al 2013; Woodward et al 2015). This study investigates brain cell transcriptional responses to nanoscale particulate matter (nPM) from urban TRP in mixed glial cultures (astrocytes:microglia, 3:1). The nPM from a local freeway is a subfraction of TRP, consisting of particles < 200 nm diameter, that was eluted from Teflon filters (Morgan et al 2011). Lipopolysaccharide (LPS, an endotoxin) was used for comparison with known inflammatory transcriptional responses. Mixed glia from neonatal rat cerebral cortex was treated with nPM (12ug/ml, 24 hours) and LPS (100ng/ml, 48 hours) and total RNA analyzed by Affymetrix Rat 230 2.0 Array. In nPM treated samples, 941 genes were upregulated, and 1089 downregulated vs. LPS, which had 615 upregulated genes, and 717 downregulated. Shared responses include 294 upregulated and 235 downregulated. Gene Ontology and KEGG pathway analysis showed large scale activation of numerous immune and stress pathways for both nPM and LPS treatment. The "response to tumor necrosis factor" and "response to interferon-gamma" were especially enriched in the altered transcripts shared by both treatments. A subset of genes was confirmed by q-PCR. Gene expression of tumor necrosis factor (TNF, 6.0 fold change for nPM) and receptor subunit (TNFrSF9, 7.5 fold change for nPM) were upregulated, while receptor associated factors TRAf6 and TRAF3ip were downregulated in nPM (0.4 and 0.3 fold change), yet unchanged in LPS treatment. Different responses to nPM and LPS indicate TRP-specific inflammatory responses that are separate from pathogen-generated LPS and other endotoxins. This microarray analysis provides a first step in identifying the specific gene transcripts and pathways involved in cellular response to direct nPM exposure, and gives new candidates for analysis of *in vivo* genomic responses to TRP.

Disclosures: E. Bacon: None. **N. Woodward:** None. **M. Levine:** None. **C. Sioutas:** None. **T. Morgan:** None. **C. Finch:** None.

Poster

768. Cellular Mechanisms of Degeneration and Inflammation in Models of Neurodegenerative Disease

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 768.09/D16

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: SEP-CONACYT Nº 157548.

Title: Evaluation of inflammation-related genes polymorphisms in Mexican with Alzheimer's disease: a pilot study

Authors: D. TORAL-RIOS[1], O. ROSAS-CARRASCO[3], F. MENA-BARRANCO[4], D. FRANCO-BOCANEGRA[5], M. MERAZ-RÍOS[2], *V. CAMPOS-PEÑA[6];
[1]Fisiología, Biofísica y Neurociencias, [2]Biomedicina Mol., Ctr. de Investigación y de Estudios Avanzados del IPN, Mexico City, Mexico; [3]Inst. Nacional de Geriatría, Mexico City, Mexico; [4]Hosp. Regional de Alta Especialidad de Ixtapaluca, Estado de México, Mexico; [5]Univ. Nacional Autónoma de México, Mexico City, Mexico; [6]INSTITUTO NACIONAL DE Neurología Y Neurocirugía, MEXICO CITY, Mexico

Abstract: Amyloid peptide is able to promote the activation of microglia and astrocytes in Alzheimer's disease (AD), and this stimulates the production of pro-inflammatory cytokines. Inflammation contributes to the process of neurodegeneration and therefore is a key factor in the development of AD. Some of the most important proteins involved in AD inflammation are: clusterin (CLU), complement receptor 1 (CR1), C reactive protein (CRP), tumor necrosis factor α (TNF-α), the interleukins 1α (IL-1α), 6 (IL-6), 10 (IL-10) and cyclooxygenase 2 (COX-2). In particular, COX-2 is encoded by the prostaglandin-endoperoxide synthase 2 gene (PTGS2). Since variations in the genes that encode these proteins may modify gene expression or function, it is important to investigate whether these variations may change the developing AD. Objetive: The aim of this study was to determine whether the presence of polymorphisms in the genes encoding the aforementioned proteins is associated in Mexican patients with AD. Method: Fourteen polymorphisms were genotyped in 96 subjects with AD and 100 controls by qPCR; the differences in allele, genotype and haplotype frequencies were analyzed. Additionally, an ancestry analysis was conducted to exclude differences in genetic ancestry among groups as a confounding factor in the study. Results: Significant differences in frequencies between AD and controls were found for the single nucleotide polymorphism (SNP) rs20417 within the PTGS2 gene (p= <0.0001**). Ancestry analysis revealed no significant differences in the ancestry of the compared groups, and the association was significant even after adjustment for ancestry and correction for multiple testing, which strengthens the validity of the results. We conclude that this polymorphism plays an important role in the development of the AD pathology and further studies are required, including their proteins

Disclosures: D. Toral-Rios: None. **O. Rosas-Carrasco:** None. **F. Mena-Barranco:** None. **D. Franco-Bocanegra:** None. **M. Meraz-Ríos:** None. **V. Campos-Peña:** None.

Poster

768. Cellular Mechanisms of Degeneration and Inflammation in Models of Neurodegenerative Disease

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 768.10/D17

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Title: Amyloid β and LPS inhibition of TGF-β signaling in primary rat microglia

Authors: K. O. AFFRAM, K. MITCHELL, S. GOPALASUBRAMANIAN, *A. J. SYMES; Pharmacol., USUHS, Bethesda, MD

Abstract: Persistent microglial activation and chronic neuroinflammation following CNS injury may contribute to long term detrimental sequelae of traumatic injury such as neurodegeneration and seizures. Reduction of this chronic neuroinflammation would therefore be beneficial to improved recovery from injury. TGF-β is a key anti-inflammatory cytokine that could reduce microglial activation and lessen neuroinflammation. We therefore wanted to determine whether TGF-β signaling is perturbed in microglia resulting in a reduction in its anti-inflammatory ability. Indeed, dysfunction of TGF-β signaling has been associated with prolonged neuroinflammatory states in neurodegenerative diseases including Alzheimer's disease. We previously have used LPS as an inflammatory stimulus in microglia, and shown that LPS treatment of primary rat microglia did result in reduced TGF-β signaling. We now have investigated the pathways that mediate this reduction of TGF-β signaling in LPS treated microglia. We also have determined that amyloid β (Aβ) treatment of microglia similarly reduces TGF-β signaling. TGF-β signals through binding to the TβRII receptor, complexing with TβRI to transduce signal. We found that LPS and Aβ dose dependently reduce TβR1 and TβRII mRNA in primary microglia thereby reducing the amount of receptor available to transduce TGF-β signals. To determine the effect of microglial activation on TGF-β mediated gene induction, we pretreated primary microglia with LPS or Aβ overnight followed by TGF-β for 6 hrs. LPS and Aβ reduced induction of the TGF-β induced genes, smad6 and TβR1. To determine which pathways may be involved in this effect, we used a series of pharmacological inhibitors of different pathways. Inhibition of the NFκb pathway (by BAY 11-7082) but not the MAP Kinase (by PD 98059) or IRF3/7 (by BX-795) pathways, prevented LPS and Aβ mediated repression of TβR1 mRNA expression. We also showed that LPS and Aβ treatment resulted in induction of mRNA encoding bambi and snoN, inhibitors of the TGF-β signaling pathway, providing a different mechanism for repression of TGF-β signaling. Finally we showed through propidium iodide cell cycle analysis that Aβ reduced TGF-β mediated microglial death enabling more microglia to survive. In conclusion, the TGF-β signaling pathway is reduced during activation of microglia with LPS or Aβ through NF-kB dependent pathways. Understanding the mechanisms

involved in dysregulation of TGF-β and other anti-inflammatory pathways during neuroinflammation could point to important therapeutic targets for chronic neuroinflammation.

Disclosures: **K.O. Affram:** None. **K. Mitchell:** None. **S. Gopalasubramanian:** None. **A.J. Symes:** None.

Poster

768. Cellular Mechanisms of Degeneration and Inflammation in Models of Neurodegenerative Disease

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 768.11/D18

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Title: Generation of a floxed human/mouse-chimeric P2X7 receptor mouse

Authors: *T. KHAYRULLINA, A. T. HOPPER, L. DORLEUS, S. B. PODA, R. G. W. STAAL, P. D. WES, T. MÖLLER;
Lundbeck Res. USA, Paramus, NJ

Abstract: Pharmacological differences between rodent and human P2X7 receptor make preclinical studies of P2X7 receptor antagonist efficacy and safety challenging. Most currently available P2X7 receptor inhibitors show a 100-300 fold difference in activity between rodent (mouse and/or rat) and human P2X7 receptors. To overcome this significant hurdle in drug development we have generated a mouse were the endogenous P2X7 receptor gene has been replaced by a humanized version. Given the complexity of the rodent P2X7 receptor gene structure and regulation, simple replacement of the entire P2X7 receptor gene is unlikely to achieve the desired result. To address these issues in a systematical way we first generated a recombinant mouse/human chimeric P2X7 receptor, carrying the human extracellular domain and the mouse intramembrane and intracellular domains. This P2X7 receptor chimera maintained human pharmacological properties, while signaling effectively in mouse cells. Careful selection of genomic integration sites for generation of mice carrying the humanized chimera predicts mouse expression patterns. Addition of LoxP sites to the insert allows for cell specific excision (GFAP-Cre = astrocytes, CXCR1-Cre = microglia) of the chimeric P2X7 receptor for validation experiments. P2X7 receptor chimeric mice are viable and fertile. The detailed characterization of these mice is ongoing.

Disclosures: **T. Khayrullina:** None. **A.T. Hopper:** None. **L. Dorleus:** None. **S.B. Poda:** None. **R.G.W. Staal:** None. **P.D. Wes:** None. **T. Möller:** None.

Poster

768. Cellular Mechanisms of Degeneration and Inflammation in Models of Neurodegenerative Disease

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 768.12/D19

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: Sidra Medical and Research Center provides the work station to process the MRI data.

Title: Analysis of cortical thickness in patients with Acute-on-chronic liver failure

Authors: *S. K. YADAV[1], M. RANGAN[2], V. A. SARASWAT[2], E. WANG[1], F. MARINCOLA[1], R. K. GUPTA[3], M. HARIS[1];
[1]Sidra Med. and Res. Ctr., Doha, Qatar; [2]Dept. of Gastroenterology, Sanjay Gandhi Post Grad. Inst. of Med. Sciences,, Lucknow, India; [3]Fortis Mem. Res. Inst., Gurgaon, Delhi, India, India

Abstract: Acute-on-chronic liver failure (ACLF) often presents with liver failure as the first evidence of liver disease, manifested by serious complications such as hepatic encephalopathy (HE). This syndrome is generally thought that results from neuronal dysfunction, morphological changes in astrocytes, and neuronal loss leads to functional deficits of varying severity. Neuroimaging techniques including diffusion tensor imaging and MR spectroscopy have been used to characterize the brain tissue injury and altered cerebral metabolites in these patients. However, except for nature of tissue changes and metabolites alteration, regional cortical thickness integrity in ACLF is unknown. Here, we have evaluated the cortical thickness in patients with ACLF and compared the changes with normal healthy volunteers. In the current study, 10 patients with ACLF and 8 healthy controls were studied. Magnetic resonance imaging (MRI) was performed at 3-T clinical MR Scanner using a standard quadrature head coil. Conventional T2- and T1-weighted imaging and high-resolution T1-weighted structural imaging were performed on each subject. We used high-resolution T1-weighted structural images for measuring regional cortical thicknesses in ACLF and control subjects using FreeSurfer. Reduced cortical thicknesses were observed on left hemisphere in insular cortex, inferior temporal, and pre-central regions, whereas on right hemisphere, superior temporal, parstriangularis, and post-central regions showed reduced cortical thickness. These multiple brain sites are involved in regulating various functions including cognitive, autonomic, language, visual sensory and motor functions. We suggest that neuronal loss and decreased cellular density due to increased cerebral hyperammonemia, proinflammatory cytokines and free radicals might be possible reasons for reduced cortical thickness in these patients. Further, study in animal model may useful to assess this correlation, which may provide more accurate explanation for the reduced cortical thickness.

Nevertheless, the current method may easily implement on clinical scanner to evaluate and monitor the brain tissue changes in patients with liver failure during the course of treatment.
Support: Sidra Medical and Research Center provides the work station to process the MRI data.

Disclosures: S.K. Yadav: None. **M. Rangan:** None. **V.A. Saraswat:** None. **E. Wang:** None. **F. Marincola:** None. **R.K. Gupta:** None. **M. Haris:** None.

Poster

769. Neuro-Oncology II

Location: Hall A

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Topic: C.12. Neuro-Oncology

Support: NSC 102-2320-B-039-026-MY3

NSC 103-2811-B-039-021

TTCRD103-18

MOHW104-TDU-B-212-113002

Title: Regulatory effects of VEGF/HO-1 signaling pathway on BDNF-induced cell migratory activity

Authors: *C. LIN[1], S.-M. HUANG[2], H.-Y. LIN[3], W.-L. YEH[4], D.-Y. LU[3];
[1]Sch. of Medicine, China Med. Univ., Taichung, Taiwan; [2]Dept. of Community Med., Preventive medicine center,Taichung Tzu Chi Hosp., Taichung, Taiwan; [3]Grad. Inst. of Neural and Cognitive Sciences, China Med. Univ., Taichung, Taiwan; [4]Dept. of Cell and Tissue Engin., Changhua Christian Hosp., Changhua, Taiwan

Abstract: Brain-derived neurotrophic factor (BDNF) expression was significantly enhanced with increasing differentiation of colon cancer and also increased with the advancing of the clinical staging. The co-expression of BDNF and TrkB receptor in colon cancer patients was found to be significantly associated with synchronous liver metastasis and peritoneal metastasis. In the presence of BDNF, the migratory activities of colon cancer cells, HCT116 and SW480, were found to be significantly enhanced. Our previous study reported that VEGF-VEGF receptor interaction promotes cancer motility. In this study, we found that the expression of VEGF was increased in response to BDNF stimulation. The enhancement of BDNF-induced cancer cell migration was antagonized by administrating a VEGF-neutralizing antibody. Hemeoxygenase

(HO)-1 is known to be involved in the development and progression of tumors. Expression of HO-1 was also elevated in response to BDNF stimulation, while BDNF-induced increase of cell migration was antagonized by inhibition of HO-1. Moreover, inhibition of HO-1 effectively reduced the BDNF-enhanced VEGF expression. These results indicate that BDNF enhances migration of cancer cells by regulation of VEGF/HO-1 signaling pathway. Our present study may provide insights to molecular mechanisms underlying how BDNF, VEGF/HO-1 promote cancer cell motility.

Disclosures: **C. Lin:** None. **S. Huang:** None. **H. Lin:** None. **W. Yeh:** None. **D. Lu:** None.

Poster

769. Neuro-Oncology II

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 769.02/D21

Topic: C.12. Neuro-Oncology

Title: Executive functions and laterality in patients with frontal tumor

Authors: *L. V. ORTEGA LEONARD[1,2], Y. DEL RÍO-PORTILLA[1];
[1]Fac. of Psychology Sleep Lab., Natl. Autonomous Univ. Of Mexico, Mexico city, Mexico;
[2]Cognition and Behavior Unit, Natl. Inst. of Neurol. and Neurosurg., Mexico City, Mexico

Abstract: Objective Evaluate executive functions in patients with frontal cerebral tumors. Method Twelve patients with diagnosis of frontal meningioma tumor type classified according to the anatomical location and a group of twelve healthy control participants matched for age, gender and education were evaluated. For the assessment of Executive Functions (EF) the following tests were applied: Backward digit span, Backward Corsi block test, Verbal fluency (semantic and phonemic), Tower of London-Drexel University version (TOL-DX), Trail Making Test (TMT) A and B, Stroop Test, Wisconsin Card Sorting test (WCST), Iowa Gambling Task (IGT), Exam Kenningar for exploration of Metaphorical Thinking. Results Comparisons among patient and healthy control groups revealed the following: 1) no significant difference was found for age and education and 2) in EF, the control group had higher scores on all tests, however statistical significant differences were found in the following tests: backward Corsi block test (p=0.04), semantic fluency (p=0.007), time of execution (p=0.009) and resolution (p=0.015) of the TOL-DX, time (p=0.004) and total errors of the TMT B (p=0.3), Stroop test (p=0.001), time of the IGT (p=0.05) and correct answer of the Kenningar Exam (p=0.02). In comparison, executive functioning related to laterality of tumors, significant differences were found in Stroop

Test (p=0.01) obtaining a higher score in patients with right lobe tumor and the number of attempts in the WCST (p=0.02) was higher in patients with left lobe tumor. Analysis between the medial, lateral and orbitofrontal regions revealed: 1) significant difference in the cognitive flexibility (correct answers of the WCST) in patients with orbitofrontal tumor have higher scores (p = 0.02), 2) in decision-making, patients with fronto-lateral tumor showed a greater number of choices of deck 3 (advantageous) in the IGT (p = 0.02). Conclusions One way to approach the knowledge of cognitive processes is by studying the functional changes in patients with brain damage. Differences in performance in tests of executive functioning were observed in patients with frontal brain tumors compared to healthy controls. Also, the execution is different between patients with right and left tumor, reinforcing differences in hemispheric localization. The results provide a better understanding of the brain executive dysfunctions caused by frontal cerebral tumors to thereby guiding more timely and effective intervention. Laura Victoria Ortega-Leonard was granted by CONACYT during her Master Degree in the Clinical Neuropsychology Residency, Faculty of Psychology and was partially granted by DGAPA, UNAM.

Disclosures: L.V. Ortega Leonard: None. **Y. del Río-Portilla:** None.

Poster

769. Neuro-Oncology II

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 769.03/D22

Topic: C.12. Neuro-Oncology

Title: Development of highly potent, selective BET bromodomain inhibitors that are CNS penetrant and effective in rodent models of brain cancer

Authors: J. ALBERT[1], A. JOHNSTONE[3], C. PENAS[3], V. STATHIAS[3], S. BROTHERS[3], N. AYAD[3,2], S. JOHNSTONE[1], *C. R. WAHLESTEDT[3];
[1]Chem., IntelliSyn Pharma, Montreal, QC, Canada; [2]Chem., IntelliSyn Pharma, Montreal, QC; [3]Psychiatry and Behavioral Sci., Univ. of Miami, Miami, FL

Abstract: Numerous highly potent, highly selective BET inhibitors have emerged and some (e.g. IBET-762) have advanced to clinical trials. We aimed to develop BET inhibitors as drug for untreatable forms of brain cancer including GBM (glioblastoma multiforme) and metastatic brain cancer. Unfortunately, we found that they are poorly suited as drugs for any indications that require high CNS drug exposure because they have high susceptibility to efflux transporters and low passive cellular permeability. To improve CNS penetration, we employed a structure-based design approach that involved (1) disrupting key transporter pharmacophore points and (2)

altering the physical properties to improve cellular permeability. In this manner we have identified EP313 which has strong potency (BRD4 IC50 7 nM), low efflux, high permeability moderate oral bioavailability in mouse (59%) and high CNS exposure. EP313 shows antiproliferative effects in TMZ-resistant cancer patient stem cell lines and dose-dependent tumor reduction in nu/nu mice that were centrally transplanted with luciferase-expressing GBM cell xenografts.

Disclosures: **J. Albert:** A. Employment/Salary (full or part-time):; IntelliSyn. **A. Johnstone:** None. **C. Penas:** None. **V. Stathias:** None. **S. Brothers:** None. **N. Ayad:** None. **S. Johnstone:** A. Employment/Salary (full or part-time):; IntelliSyn. **C.R. Wahlestedt:** None.

Poster

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Topic: C.12. Neuro-Oncology

Support: Grant-in-Aid for Exploratory Research, the Japan Society for the Promotion of Science

Cancer Consortium, Kansai Medical University

Title: Selective siRNA-mediated suppression of nSR100 (SRRM4) induces the cell death of small cell lung cancer

Authors: ***M. SHIMOJO**[1], Y. SHUDO[2], S. ITO[3];
[2]Psycosomatic Med., [3]Med. Chem., [1]Kansai Med. Univ., Hirakata/Osaka, Japan

Abstract: Small cell lung cancer (SCLC) is a highly malignant form of cancer, which originates from primitive neuroendocrine cells in the lung. SCLC cells express several autocrine neurotransmitters and neuropeptides and their respective receptors. It was reported that the expression of these neuronal markers is regulated by RE1-silencing transcription factor (REST). In SCLC cells, an SCLC-specific isoform of REST (sREST) is highly expressed while full-length REST expression is too low to detect, suggesting that the expression of sREST correlates with the pathogenesis of SCLC. We previously reported that the neural-specific SR-related protein of 100 kDa (nSR100) abnormally activates the alternative splicing of REST (Mol. Cancer Res. 11, 1258 (2013)) in SCLC cells. Repression of nSR100 by specific siRNAs affected the expression of REST and sREST proteins and mRNAs in SCLC cells, while no change in NSCLC cells. Expression of siRNAs showed low viability of SCLC cells, suggesting apoptosis induced.

There is recently increasing evidence that miRNA expression plays a fundamental role in gene regulation and may contribute substantially to cancer progression through translational repression. We analyzed the miRNA expression in SCLC cells using microarray analysis, suggesting that some of down-regulated miRNAs are predicted to interact with nSR100 mRNA. Analysis of these down-regulated miRNAs in patients' serum showed that the expression of a specific miRNA was significantly higher in SCLC patients than in other tumor patients. Furthermore we have found the miRNAs in SCLC patients' serum were selectively incorporated in the exosome. SCLC cells cultured on Matrigel in the condition which causes the up-regulation of nSR100 expression showed that the secretion of the miRNA in exosome was increased, while the intracellular miRNA significantly decreased. Taken together these results suggest that the miRNA targeting nSR100 might be a novel SCLC-specific biomarker. Overall the results of this study highlight the important role of nSR100 targeting apoptosis in SCLC.

Disclosures: **M. Shimojo:** None. **Y. Shudo:** None. **S. Ito:** None.

Poster

769. Neuro-Oncology II

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Program#/Poster#: 769.05/D24

Topic: C.12. Neuro-Oncology

Support: Fonds de recherche du Québec - Nature et technologies (Grant No 172009)

Title: Neuroplasticity changes in rat brain following targeted Gamma Knife irradiation

Authors: ***J. CONSTANZO**[1], M. DESCOTEAUX[2], M. LEPAGE[1], L. TREMBLAY[1], M. DUMONT[2], J.-M. LONGPRÉ[3], K. KIRBY[3], S. GEHA[4], L. MASSON-COTÉ[1], P. SARRET[3], B. PAQUETTE[1];
[1]Nuclear medicine and radiobiology, [2]Computer science department, [3]Physiol. and biophysics department, [4]Pathology department, Sherbrooke Univ., Sherbrooke, QC, Canada

Abstract: Purpose: Stereotactic radiosurgery (SRS) is a well-established treatment for many types of brain tumors. However, surrounding healthy tissues may also receive a significant radiation dose during SRS. This can lead to brain swelling, necrosis, and neuronal dysfunction, thus inducing delayed adverse effects such as cognitive decline and stroke-like symptoms. We thus propose to use neuroimaging (diffusion MRI (dMRI)) and behavioral assessment tools to enhance our understanding of the neuroplasticity changes associated with brain irradiation. Results: Thirty male Fisher rats were irradiated using a targeted irradiation in the primary

somatosensory area (S1), hippocampus and primary motor cortex (M1) of the right hemisphere. Using the Leksell Gamma Knife Perfexion®, the mean deposited dose into the S1, hippocampus and M1 structures were respectively, 113 ± 4 Gy, 24 ± 10 Gy, 41 ± 8 Gy. At different time points after irradiation, rats were scanned with a small animal MRI scanner (7T) using high angular resolution dMRI (HARDI) to assess the integrity of neuronal interconnections. HARDI tractography and diffusion metrics revealed displacements and breakdown in neuronal pathways. Also, brain-region specific sensitivity to irradiation was determined using different behavioral tests assessing: i) motor function (Rotarod and Actimetry), which revealed that brain irradiation did not affect motor performance (M1-related), ii) the anxiety-like behaviors and learning/memory performances (Elevated plus maze and Morris water maze), which were significantly decreased in rats exposed to gamma irradiation, probably reflecting right amygdala and hippocampus alterations, and iii) sensory pain behaviors (formalin test) that revealed dysfunction in descending pain inhibition (S1-related). In addition, myelin sheath damage and reactive astrogliosis were found around the radionecrosis in the surrounding white matter by immunohistochemistry. Conclusion: Altogether, our results revealed that SRS treatment induces region-specific plasticity (i.e. structural and function changes), as demonstrated by neuronal matrix remodeling using diffusion MRI and appropriate HARDI reconstruction, and changes in behavioral responses.

Disclosures: **J. Constanzo:** None. **M. Descoteaux:** None. **M. Lepage:** None. **L. Tremblay:** None. **M. Dumont:** None. **J. Longpré:** None. **K. Kirby:** None. **S. Geha:** None. **L. Masson-Coté:** None. **P. Sarret:** None. **B. Paquette:** None.

Poster

769. Neuro-Oncology II

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 769.06/D25

Topic: C.12. Neuro-Oncology

Support: NIH RO1-CA166749-02S1

Title: Mechanisms underlying the sorting of growth factor receptors

Authors: *M. B. GIREUD[1,2], A. BEAN[3,4,2];
[1]Neurobio. and Anat., Ut Houston Hlth. Sci. Ctr., Houston, TX; [2]Univ. of Texas Grad. Sch. of Biomed. Sci., Houston, TX; [3]Neurobio. and Anat., UT Houston Hlth. Sci. Ctr., Houston, TX; [4]Pediatrics, M.D. Anderson Cancer Ctr., Houston, TX

Abstract: Membrane proteins (e.g. transporters, ion channels, receptors) reside on the cell surface and influence cellular behavior in response to extracellular signals. Regulating their residence time on the cell surface can modify the activity of these membrane proteins and allow for cellular adaptation according to environmental conditions. Removal of membrane proteins by endocytosis follows a canonical itinerary in which cargo passes through morphologically and biochemically defined organelles. After internalization from the plasma membrane and transport from early to late endosomes, proteins destined for degradation in the lysosome are internalized into the lumen of late endosomes via membrane invagination and vesicle fission. The resulting organelle, the multivesicular body (MVB), is characterized by a limiting membrane and the presence of internal vesicles. Proteins that are sorted into internal MVB vesicles are subject to degradation upon endo-lysosomal fusion, while those that remain on the limiting endosomal membrane are recycled. Ubiquitin facilitates the sorting of protein cargo into the internal vesicles of the MVB by allowing their interaction with components of the sorting machinery, the endosomal sorting complexes required for transport (ESCRTs). Defects in intracellular trafficking pathways can modulate the kinetics of membrane protein signaling by altering their surface expression that can contribute to the pathogenesis of diseases including various cancers and neurodegenerative diseases. To examine the mechanisms underlying endosomal sorting, we have established a cell-free assay that measures both MVB formation and the sorting of a cargo protein into the endosomal lumen (degradation), as well as vesicles that bud from endosomal membranes (recycling). Both sorting events are dependent on cytosolic proteins. We have isolated and characterized both vesicles and cargo that are sorted from endosomal membranes and have examined the cytosolic components required for both the inward and outward sorting events. These experiments have revealed requirements for various cytosolic proteins and suggest that the mechanisms underlying these two sorting events may be distinct. These mechanistic differences could possibly be exploited for therapeutic benefit in diseases such as glioblastoma, where EGFRviii is though to be continuously recycled resulting in uncontrolled cell growth.

Disclosures: **M.B. Gireud:** None. **A. Bean:** None.

Poster

769. Neuro-Oncology II

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 769.07/D26

Topic: C.12. Neuro-Oncology

Support: Rosenblatt family donation to the St. Peters Hospital Foundation

Children's Tumor Foundation

Title: Neural etiology and characteristics of neurofibromas in human neurofibromatosis type 1 patients

Authors: *G. HOUK[1], J. P. WYMER[2], P. J. ALBRECHT[1], P. KNIGHT[3], H. WEINBERG[4], F. L. RICE[1];
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Abstract: In addition to neurofibroma tumors, NF1 patients experience chronic pain from unafflicted skin locations. With IRB approval from St. Peters Hospital, Albany, potential sources of this pain were investigated by multi-molecular immunofluorescence assessments of 3mm skin punch biopsies taken from palmar and dorsal hypothenar sites on the hand and from the distal leg of 19 NF1 and 16 control adult subjects. Labeling of all innervation with anti-protein-gene-product 9.5 (PGP) revealed a single, discrete, miniscule neuroma in at least 1 of the 3 biopsies from most of the NF1 subjects. Nearly all of these “microneuroma” were sprouting from the margin of specific structures - dermal papillae, sweat glands, arterioles, hair-follicles - that are normally targets of dense, multiple types of innervation, which was mostly still intact. The densely concentrated fibers had neurochemical features of C-fibers that expressed growth associated protein (GAP43) and lacked neuropeptides. Intermingled S100-labeled Schwann cells were in proportion to the fibers and lacked markers indicative of excessive proliferation thought to be the genesis of neurofibromas. In contrast to Schwannomas, neurofibromas are known to contain other cell components leading us to hypothesis that the microneuromas and their affiliated target structure may be the sites of neurofibroma genesis. To test this, we examined 20 overt small, neurofibromas (2-5mm) from 2 patients. Most contained evidence of a core structure, such as an overgrown hair follicle from which excessive, compact innervation spread outwards (like a mushroom cap) just below the subepidermal compact papillary dermis. GAP43-labeling revealed that the expanding nerve fibers remained extremely dense in the larger neurofibromas, where PGP expression diminished and failed to reveal most of the innervation. Schwann cells increased intermingled with and in proportion to (but not in excess of) the sprouting innervation. These results suggest that the etiology of neurofibromas may primarily be sprouting of small number axon terminals instead of excessive Schwann cell proliferation.
Supported by a donation of the Rosenblatt family to the St. Peters Hospital Foundation and by the Children’s Tumor Foundation.

Disclosures: G. Houk: None. **J.P. Wymer:** None. **P.J. Albrecht:** None. **P. Knight:** None. **H. Weinberg:** None. **F.L. Rice:** None.

Poster

769. Neuro-Oncology II

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 769.08/D27

Topic: C.12. Neuro-Oncology

Support: 232644

Title: New model of nociception induced by bone metastasis in rat femur: behavioral analysis

Authors: *J. N. CORONA-RAMOS[1], O. A. JARAMILLO-MORALES[2], J. V. ESPINOSA-JUAREZ[2], M. DÉCIGA-CAMPOS[3], P. GARCIA-LOPEZ[4], F. J. LOPEZ-MUÑOZ[2];
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Abstract: In the majority of cases of patients with metastatic cancer of unknown primary origin, there is no an adequate therapeutic treatment. The objective of this study was to develop a model of nociception induced by bone metastasis through inoculating glioma within Wistar rat femur. The different stages of the cancer depended on the amount of inoculated cells, we injected between 50,000 and 100,000 cancer cells into the femur. It was used the von Frey test, Hargreaves plantar test, and for detection of spontaneous pain, the animals were filmed by 30 minutes and were quantified the number of forelimbs shake. Using this model, we could showed that glioma can remain in the bone marrow and have the capacity to produce osteolysis, bone fracture and peripheral and central pain, in similar way as it has been reported with bone metastasis caused by prostate cancer, breast and lung. The analysis of results showed changes in mechanical and thermal hypersensitivity and spontaneous pain, these behavioral changes occurred significantly after 14 days post-inoculation. We conclude that this model could be an excellent tool, showing for the first time that glioma may be maintained by the skeletal system, producing changes in the mechanical and thermal hypersensitivity and spontaneous nociception.

Disclosures: J.N. Corona-Ramos: None. **O.A. Jaramillo-Morales:** None. **J.V. Espinosa-Juarez:** None. **M. Déciga-Campos:** None. **P. Garcia-Lopez:** None. **F.J. Lopez-Muñoz:** None.

Poster

769. Neuro-Oncology II

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 769.09/D28

Topic: C.12. Neuro-Oncology

Title: The interaction of ETS domain protein Elk-1 with mitotic kinases and its phosphorylation in brain tumor model cells

Authors: *O. ARI UYAR[1], O. DEMIR[2], B. YILMAZ[2], I. AKSAN KURNAZ[3];
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Abstract: Elk-1 is a member of Ets (E twenty-six) oncogene family of transcription factors that have important roles in development and disease. Elk-1 is known to be phosphorylated by PKC, MAPK and PI3K pathways and any abnormalities present in these pathways as well as changes in the protein structure and expression can give an advantage for the growth of tumors. Through various projects in our laboratory, we have identified a different mitotic role of the mitogenic transcription factor Elk-1 in various brain tumor model cell lines such as glioma, glioblastoma and neuroblastoma. Elk-1 is able to bind microtubules and microtubule related motor proteins in a phosphorylation dependent manner. The mitotic localization of Elk-1 transcription factor in mitotic spindle poles in prophase and metaphase, in midzone in anaphase, and in spindle midbody in telophase / cytokinesis transition has been demonstrated for the fist time which is most likely related to its non-transcriptional mitotic role. This mitotic localization of Elk-1 and its interaction with mitotic motor proteins indicates a non-transcriptional mitotic role of Elk-1. In the light of the in silico analysis within this framework has elucidated a number of potential mitotic kinase phosphorylation motifs on Elk-1 such as T133, S200 and S202 for Cdks, S106, T108 and S198 for Plk1, T199 and S200 for Aurora A kinase. Mitotic kinases have pivotal roles during regulation of this mechanism as well as cell cycle progression, centrosome maturation and microtubule dynamics that is pivotal for the formation of bipolar mitotic spindle and accurate segregation of chromosomes. Any abnormalities in the function of these kinases may lead to uncontrolled proliferation, aneuploidy, and genetic instability that lead cancer development and progression. Elucidating the possible interaction between Elk-1 and target mitotic kinases may help to understand the potential role of Elk-1 during mitosis and its contribution to brain tumor formation.

Disclosures: **O. Ari Uyar:** None. **O. Demir:** None. **B. Yilmaz:** None. **I. Aksan Kurnaz:** None.

Poster

769. Neuro-Oncology II

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 769.10/D29

Topic: C.12. Neuro-Oncology

Title: Effect of tumor characteristic and location on language activation

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Abstract: Introduction: Functional MRI can be an important tool to visualize and study brain activity in patients with a brain tumor. For instance, fMRI could be used to detect abnormal activity in specific locations. However, this is only valid if the overall pattern of activity is not substantially changed by the presence of the tumor. However, in order to interpret patterns of brain activity, it is important to know that the tumor does not change the activity pattern to such an extent that for instance spatial normalization might not be a valid tool anymore. In this study we tested the robustness of the activity pattern associated with a verb generation paradigm, a common and much applied clinical fMRI paradigm. Method: Patients with either a LGG on the left (N = 38) or right hemisphere (N = 17), or a HGG in the left (N = 31) or right hemisphere (N = 28) were included in the study. Al patients performed a verb generation task that is commonly used in clinical fMRI. All fMRI scans were produced using a 3T Philips scanner (PRESTO pulse sequence, voxelsize: 4x4x4 mm, TE: 1.5 sec), corrected for movement, and spatially smoothed (FWHM: 12mm). After preprocessing, a GLM was performed to extract beta scores per voxel, indicating level of involvement in the task. We spatially normalized all b-maps from all subjects in to MNI space using FSL software. Using the AAL atlas, we calculated the average activity for all 90 cortical and subcortical regions per subject and tested for differences in age as well as differences in activation between the four groups (ANOVA, $p< 0.01$, uncorrected). Results: Age of subjects differed significantly between groups ($F = 11.2$; $P < 0.01$), as HGG patients were significantly older (50.6 years) than LGG patients (37.1 years). None of the 90 analyzed ROIs showed a significant difference between the groups. Discussion: Results indicate that the characteristic (low grade or high grade) and hemisphere did not significantly affect the activity pattern related to verb generation, using common analysis techniques for fMRI such as linear spatial normalization after spatial smoothing. This result indicates that group level statistics based on common techniques are also valid for patient populations with a LGG or HGG tumor in left or right hemisphere.

Disclosures: J.M. Jansma: None. **G. Rutten:** None.

Poster

769. Neuro-Oncology II

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Program#/Poster#: 769.11/D30

Topic: C.12. Neuro-Oncology

Support: Swedish Childhood Cancer Foundation (PROJ13/027)

Swedish Cancer Foundation (CAN 2014/707)

Swedish governmental grants to scientists working in health care (ALFGBG-429271)

Title: Lithium prevents irradiation-induced brain injury and long term cognitive dysfunction in the young rat

Authors: *C. ZHU[1], K. ZHOU[2], C. XIE[3], Y. ZHANG[4], T. LI[4], K. BLOMGREN[5];
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Abstract: Background: There is growing evidence that lithium (Li) is protective in a variety of brain injury paradigms. Cranial radiotherapy in children usually results in cognitive as well as hypothalamic/pituitary dysfunction. Objective: Our aim was to investigate the effects of lithium treatment on cognitive and endocrine function in the juvenile brain after irradiation. Design/Methods: Male Wistar rats were injected with 2 mmol/kg LiCl i.p. on postnatal day 7 (P7) and additional lithium injections, 1 mmol/kg, were administered at 24 h intervals for up to 14 days (until P20). On P11 the whole brain received a single IR dose of 6 Gy. Blood samples were collected from the tail vein 1, 3, and 5 weeks after IR. Results: Irradiation-induced progenitor cell death in the subgranular zone of the hippocampus was reduced by lithium treatment. Neurogenesis was reduced by irradiation but was partly rescued by lithium. Inflammation in the hippocampus at 6 h after irradiation was reduced by lithium. Body growth was reduced by irradiation, but not by lithium treatment. Thyroid-stimulating hormone and growth hormone levels were decreased in irradiated rats but not in rats treated with lithium. Motor hyperactivity and anxiety-like behavior, as well as cognitive impairment after irradiation were normalized by lithium. Conclusion: Lithium can be safely administered to prevent both short-term and long-term damage to the immature brain caused by ionizing radiation.

Disclosures: C. Zhu: None. **K. Zhou:** None. **C. Xie:** None. **Y. Zhang:** None. **T. Li:** None. **K. Blomgren:** None.

Poster

769. Neuro-Oncology II

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 769.12/D31

Topic: C.12. Neuro-Oncology

Support: NIH grant R01 AA11591

Title: Evidence for the existence of tumor stem progenitor-like cell markers and aggressive prolactin-secreting tumors in the pituitary of fetal alcohol exposed rats

Authors: S. JABBAR[1], O. GANGISETTY[1], *D. K. SARKAR[2];
[1]Animal Sci., Rutgers, the State Univ. of New Jersey, New Brunswick, NJ; [2]Rutgers, SUNJ, New Brunswick, NJ

Abstract: Prolactin-secreting pituitary tumors (prolactinomas) are the most common pituitary tumors in humans. Majority of prolactinomas are adenomas and benign and slow growing, but in some cases, they are locally aggressive and invasive. In case of malignancy and aggressive tumor, stem progenitor-like cell (cancer stem cells; CSC) serve a critical role in the tumor microenvironments and in the processes of cancer cells proliferation, migration, invasion and angiogenesis. The evidence for the existence of CSC in rat pituitary tumors still needs to be elucidated. We determined whether fetal alcohol exposure enhances the population of CSC and aggressive prolactinomas in the pituitary in response to estradiol. Pregnant Fischer 344 rats were fed between gestational days 7 and 21 with a liquid diet containing alcohol (AF), pair-fed with isocaloric liquid diet (PF), or fed ad libitum with rat chow (AD). At 60 days of age, female offspring rats were ovariectomized and received a subcutaneous estradiol implant. These rats were sacrificed at 3 months after the estradiol implants. Estradiol treatment increased pituitary weight about 5-folds in AD and PF treated groups while increased about 30-folds in the AF treated group. Pituitary tumors were collected and enzymatically digested and cultured in serum-free and phenol red-free DMEM, and supplied with EGF, bFGF, and 1X B27 supplement in ultra-low attachment 24-well plate. The growing spheres were mechanically dissociated to make serial passaging. We assayed a panel of genes related to multipotency (OCT4, NANOG, KLF4, and CD133) and found mRNA expressions were significantly higher in pituitary spheres of AF animals as compared to AD and PF groups. Differentiated tumor cells of AF animals also showed strong nuclear p53 and monoclonal Ki67 and PRL immunoreactivity, higher mRNA levels of hemorrhage-associated genes (VEGF and MMP-9), and higher cell proliferation, migration and colony formation rates as compared to control groups. These data provide evidence for the existence of CSC and possible development of aggressive prolactinomas in the pituitary after estrogen treatment in fetal alcohol exposed female rats.

Disclosures: **S. Jabbar:** None. **O. Gangisetty:** None. **D.K. Sarkar:** None.

Poster

769. Neuro-Oncology II

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Program#/Poster#: 769.13/D32

Topic: C.12. Neuro-Oncology

Support: Lynn Sage Cancer Research Foundation, T32-NS047987

R01-NR014182

Title: Hippocampal subfield deformity in breast cancer patients with self-reported cognitive concerns

Authors: *A. APPLE[1], A. J. RYALS[2], L. I. WAGNER[2,3], D. CELLA[1,2,4,3], F. J. PENEDO[1,2,3], J. L. VOSS[2,4], L. WANG[1,5,3];
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Abstract: Objective. Cancer survivors including those who received chemotherapy have lingering cognitive problems, however the anatomical basis for those cognitive problems has yet to be found. Neuroimaging studies in this population suggest gray matter volume loss in several brain regions including the temporal lobe. Clinical studies report volume loss in the hippocampus and animal models of chemotherapy report cell loss in the dentate gyrus, a subfield of the hippocampus. However, few studies have performed detailed analysis of the hippocampus and its subfields on cancer patients. This study used high-dimensional deformation mapping analysis to test whether hippocampal subfields differ in breast cancer survivors who received adjuvant chemotherapy coupled with hormone blockade therapy. Furthermore, we explored how subfield abnormalities were related to subjective self-reported concerns and objective cognitive ability. Participants and Methods. 3T MPRAGE MRI images were acquired from 16 pre-menopausal breast cancer patients and 18 healthy controls. Breast cancer patients had undergone chemotherapy within eighteen months prior to the study, and they were all receiving estrogen-blockade therapy at the time of the study. Automated high-dimensional deformation mapping was used to compare hippocampal shape differences between groups Self-reported subjective concerns were assessed with NeuroQOL and PROMIS measures, and objective cognition was assessed with the NIH Toolbox Cognition Battery. Results. Patients reported significant cognitive concerns compared to controls, but did not differ on objective tests of cognition. Groups differed significantly in hippocampal shape ($p=0.016$). Using high-dimensional

deformation mapping, we localized this difference in deformation to specific sub-regions of the hippocampus. Relative to controls, patients showed inward deformation in the right CA1, (p=0.042) the left CA2-4 + dentate gyrus (, p=0.027), and the right subiculum (p=0.022). No associations were observed between deformation and measures of cognition or self-reported cognitive concerns in patients. Conclusions. This study is the first of its kind to examine subfield deformity as it relates to cognitive function in cancer patients. Although no differences in objective cognition were observed, given the morphological changes in hippocampal structure and self reported cognitive difficulties, it is possible that the neuropsychological measures are either not sensitive enough to detect the subjective deficits that patients reported or are measuring cognitive domains not directly associated with the detected damage.

Disclosures: **A. Apple:** None. **A.J. Ryals:** None. **L.I. Wagner:** None. **D. Cella:** None. **F.J. Penedo:** None. **J.L. Voss:** None. **L. Wang:** None.

Poster

769. Neuro-Oncology II

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 769.14/D33

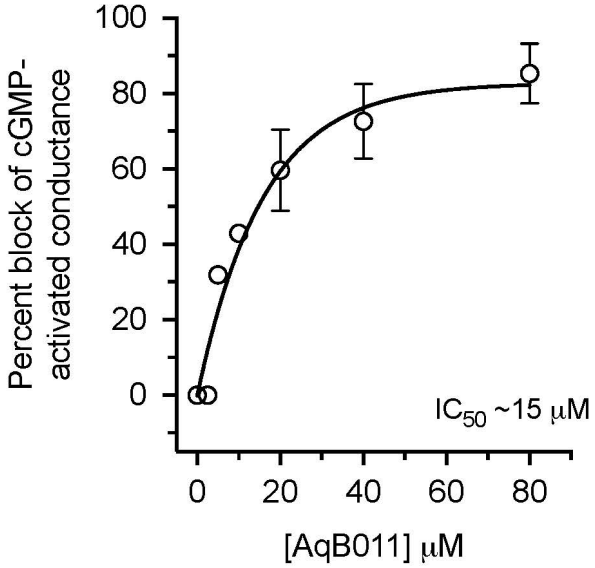
Topic: C.12. Neuro-Oncology

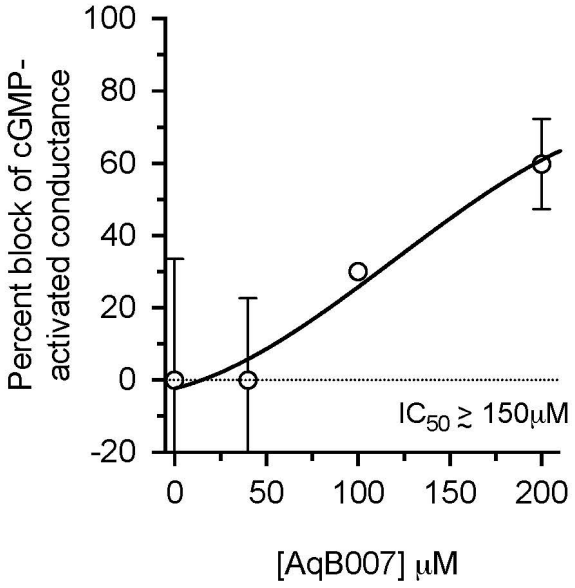
Title: Blocking Aquaporin 1 ion channel function with AqB011 could be a new therapeutic approach for preventing cancer metastasis

Authors: ***M. KOURGHI**[1], J. PEI[2], M. DE IESO[2], A. YOOL[2];
[1]Physiol., [2]The Univ. of Adelaide, Adelaide, Australia

Abstract: Aquaporins (AQPs) are members of the major intrinsic family of proteins (MIPs) that allow pathways for water flux across cell membranes. AQPs are found across different organisms at all levels of life. To date 13 mammalian members of this family have been identified, AQP0-AQP12. AQP1 is a water channel, and under permissive conditions, also functions as a nonselective monovalent cation channel activated by intracellular cGMP. AQP1 expression facilitates cancer cell migration and spread in various cancer types including glioblastoma. Wild-type human AQP1 channels expressed in Xenopus laevis oocytes were characterized by two-electrode voltage clamp and optical osmotic swelling analyses. Cell migration was performed using wound closure assay in presence of a mitotic inhibitor to distinguish motility from proliferation. The current study has characterized a series of bumetanide derivatives for blocking effects on the ion channel function of AQP1, independent of the water channel permeability. The compound AqB011 imposed the most potent block of the

AQP1 ion channel (IC50 value of 15uM) but it had no effect on the water channel activity. The order of potency was AqB001 ≤ AqB006 < AqB050 < AqB007 < AqB011. These results were consistent with in silico models predicting energetically favoured binding of the compound to the channel. AqB001 had the lowest while AqB011 possessed the highest apparent binding affinity to the channel, with likely site of interaction of AqB011 being at loop D gating domain. Furthermore AqB011 was tested on AQP1 expressing cancer cell lines and found to significantly reduce the migration ability of the cancer cells. Therefore inhibition of Aquaporin 1 could an important new therapeutic approach for reducing cancer metastasis.





Disclosures: **M. Kourghi:** None. **J. Pei:** None. **M. De Ieso:** None. **A. Yool:** None.

Poster

770. Psychosis: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 770.01/D34

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: BSI-a Johnson & Johnson Translational Innovation Fellow

Title: Conditional knockout of Ankyrin-g in mouse forebrain: potential model of bipolar disorder

Authors: *S. ZHU[1], Z. CORDNER[1], J. KIM[2], X.-F. WANG[1], M. PLETNIKOV[1], K. TAMASHIRO[1], C. A. ROSS[1];
[1]Psychiatry, The Johns Hopkins Univ., Baltimore, MD; [2]Neurosci., Johns Hopkins Univ., Baltimore, MD

Abstract: The ANK3 locus, encoding Ankyrin-G, shows genome-wide significance in GWAS for bipolar disorder, and some significance for schizophrenia. In the central nervous system Ankyrin-G mainly localizes to the axon initial segment (AIS), where action the potential is initiated and propagated. Schizophrenia postmortem brain studies indicate decreased Ankyrin-G expression at axon initial segments of pyramidal neurons in the cortex. We have established a forebrain-specific Ankyrin-G conditional knockout (KO) mouse model, in which knockout is restricted to adulthood. Behavioral characterization showed that the forebrain conditional Ankyrin-G knockout model displays increased motor activity, increased exploratory activity, and less anxiety-like behavior, reminiscent of mania. At the AIS, pyramidal neurons of the cortex have strikingly decreased GABAergic marker positive presynaptic terminals, consistent with disinhibition. Chronic application of several anti-manic agents such as Lithium and Valproic Acid at therapeutic levels ameliorated the hyperactivity. Moreover, after social defeat stress, the mice displayed depression-like behavior. This forebrain-specific Ankyrin G conditional knockout mouse model may be useful as potential model of bipolar disorder, in order to explore neurobiological mechanisms, and to develop new therapeutic strategies for bipolar disorder and possibly schizophrenia.

Disclosures: S. Zhu: None. **Z. Cordner:** None. **J. Kim:** None. **X. Wang:** None. **M. Pletnikov:** None. **K. Tamashiro:** None. **C.A. Ross:** None.

Poster

770. Psychosis: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 770.02/D35

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: SNSF #31-116689

SNSF #310030_135736/1

SNSF #51AU40_125759

Avina Foundation

Damm-Etienne Foundation

Alamaya Foundation

Title: A developmental redox dysregulation leads to impaired thalamocortical network dysfunction in a mouse model of schizophrenia

Authors: *J. H. CABUNGCAL[1], P. STEULLET[1], R. KRAFTSIK[2], T. SALT[3], M. CUENOD[1], K. Q. DO[1];
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Abstract: Dysfunction of parvalbumin-expressing fast-spiking interneurons (PVI), essential for coordinating neuronal synchrony during sensory and cognitive processing, is a hallmark in the pathophysiology of schizophrenia (SZ). Oxidative stress as observed in schizophrenia affects PVI. The effect of oxidative stress, in PVI rich brain regions, during specific developmental time windows is lacking. One PVI rich brain region of interest is the thalamic reticular nucleus (TRN), a communication and gating hub between the thalamus and the cortex. Providing evidence that oxidative stress impairs normal TRN PVI developmental trajectory and function may provide better understanding of the role of TRN in the pathophysiology of SZ, and render it a candidate for drug target. We used mice with impaired synthesis of glutathione (Gclm KO) to investigate the effect of redox dysregulation on maturation and functional integrity of PVI in the TRN at various periods of postnatal development. A developmental redox dysregulation rendered PVI highly vulnerable to oxidative stress already in juvenile age (P20), which worsened at pubertal (P40) and adulthood (P90). The perineuronal net (PNN) surrounding mature PVI was impaired at pubertal (P40). PVI with little, or no surrounding PNN, were mostly affected by

oxidative stress in adulthood (P90). Elevated levels of oxidative stress, PVI and PNN deficit in the TRN can be prevented with the anti-oxidant N-acetylcysteine treatment. Preliminary electrophysiological recording in late adolescent indicates an abnormal connectivity between the TRN and the thalamocortical neurons. Our data show that PVI and their PNN are mostly compromised at adolescent (P40), when many changes in life take place. The data also reveals early vulnerability period of PVI in the TRN to oxidative stress and the need to develop therapeutic approaches based on anti-oxidant and redox regulator compounds for preventive treatment in young at-risk subjects. These findings suggest that a developmental redox dyregulation in the TRN could play a critical role in impairing the thalamocortical gating system in animal models of SZ, which could arise from the impact of genetic abnormalities on this circuitry during the neurodevelopmental period.

Disclosures: J.H. Cabungcal: None. **P. Steullet:** None. **R. Kraftsik:** None. **T. Salt:** None. **M. Cuenod:** None. **K.Q. Do:** None.

Poster

770. Psychosis: Animal Models

Location: Hall A

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Program#/Poster#: 770.03/D36

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: Public Interest Trust Research Aid Fund for Stress-Related Diseases (with Commemoration of Imai kimi)

Research Aid Fund from Lilly

KAKENHI (18023009, 20023006, 20390098)

William Paterson University

Title: Environmental stressors induce schizophrenia-like symptoms based on genetic dysfunction of cannabinoid type 2 receptor and K-Cl cotransporter KCC2

Authors: *H. ISHIGURO[1], K. TABATA[1], A. OKABE[2], N. MOTOHASHI[1], E. S. ONAIVI[3]; [1]Univ. of Yamanashi, Chuo, Yamanashi, Japan; [2]Div. of Physiome, Dept. of Physiology, Hyogo Col. of Med., Hyogo, Japan; [3]Dept. of Biol., William Paterson Univ., Wayne, NJ

Abstract: Major depression and schizophrenia are mental health problems associated with stressful events in life based on certain genetic background. In our previous study, we have

demonstrated a high incidence of polymorphisms in the Cannabinoid CB2 Receptor gene (CNR2) and K-Cl cotransporter gene (KCC2) in schizophrenia and depression in Japanese population. The CB2 receptor has behavioral roles in response to pharmacological, immunological and psychological stresses via HPA axis. KCC2 also works in schizophrenia by modulating GABAergic neural function in brain. Therefore, we further examined a functional relationship between stressors and those molecules using those knockout mice as schizophrenia and depression models in this study. First we have confirmed that neither Cnr2 knockout mice nor Kcc2 knockout mice did not show any difference in PPI and in Zero maze test. Then we tested several stressors in mice models. Methamphetamine was injected to those mice to examine their locomotion as acute response and as reverse tolerance. The Cnr2 knockout mice, but not Kcc2 knockout mice showed more locomotive activity after the acute treatment. Kcc2 knockout mice instead showed dramatic enhancement in locomotion after development of reverse tolerance. Poly-IC was injected i.p. to Cnr2 knockout mice, and their locomotor activity was measured 72 hours after the injection and compared with those of the wild type controls. The heterozygote mice relatively reduce their locomotion in the test cage. Also heterozygote Cnr2 knockout mice show more anxiety in Zero maze than wild type after Poly-IC injection. Either Fkbp5 expression in Cnr2 knockout mice brain or Gad1 expression in Kcc2 knockout mice brain were differed after they developed behavioral phenotypes above. It was interpreted that mice with those genetic dysfunctions develop psychiatric behaviors if they experienced several stresses. Further studies are required to determine specific fragile age to the stressors based on each genetic background in the etiology of those psychiatric diseases.

Disclosures: **H. Ishiguro:** None. **K. Tabata:** None. **A. Okabe:** None. **N. Motohashi:** None. **E.S. Onaivi:** None.

Poster

770. Psychosis: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 770.04/D37

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: NIMH IRTA

Title: The relationship between parvalbumin-positive interneuron density in the auditory and frontal cortices and hearing loss in a mouse model of 22q11.2 Deletion Syndrome

Authors: *F. A. ZINNAMON[1,2], S. S. WENAS[1], K. H. WANG[2], J. F. LINDEN[1];
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Abstract: 22q11.2 Deletion Syndrome (22q11DS) is a genetic syndrome that results from a 1.5-3Mb congenital multigene deletion on the long arm of chromosome 22. Occuring in 1:4000 live births, it is the most common genetic microdeletion syndrome. Approximately 25-30% of adults with 22q11DS develop schizophrenia during adolescence or adulthood. As one of the most significant known cytogenetic risk factors for schizophrenia, 22q11DS holds the potential to provide insight into neural systems abnormalities associated with schizophrenia and genetic risk for schizophrenia. The Df1/+ mouse model of 22q11DS recapitulates many features of human 22q11DS and schizophrenia, including cognitive impairment and frequent otitis media, a middle ear disease that can cause conductive hearing loss. In other model systems, both hearing loss and schizophrenia risk factors have been shown to be associated with abnormalities in parvalbumin-positive (PV+) inhibitory interneuron circuitry in the cortex. However, the relationship between hearing loss, genetic risk of schizophrenia, and PV+ interneuron circuitry remains poorly understood. Here we explored this relationship through studies of PV+ interneuron density in auditory and frontal cortices of WT mice and Df1/+ mice with and without conductive hearing loss. Previous work has shown that approximately half of Df1/+ mice have conductive hearing loss due to otitis media; moreover, the hearing loss is frequently monaural. We tested for otitis media or hearing loss in both left and right ears of Df1/+ mice and their WT littermates, using tympanic membrane inspection and/or auditory brainstem response measurements. Then, we performed PV+ immunohistochemistry on coronal sections through the auditory and frontal cortices of the mice, and quantified PV+ interneuron density across cortical layers. Comparing results between Df1/+ and WT mice, we found significant reductions in PV+ interneuron density in Df1/+ mice, especially in middle and lower layers of the primary auditory cortex. However, among the Df1/+ mice, we also found a significant correlation between reduced PV+ interneuron density in the auditory cortex and hearing loss in the contralateral ear. The results suggest that genetic risk of schizophrenia and developmental hearing loss could interact to produce cumulative abnormalities in PV+ interneuron networks in the cortex. Implications of these findings will be discussed in light of recent neurophysiological studies in Df1/+ mice and our ongoing investigations.

Disclosures: F.A. Zinnamon: None. **S.S. Wenas:** None. **K.H. Wang:** None. **J.F. Linden:** None.

Poster

770. Psychosis: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 770.05/D38

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: A role for microRNA-206 in schizophrenia-related behaviors

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Abstract: Schizophrenia is a debilitating, heterogeneous psychiatric disorder characterized by positive symptoms such as psychosis and negative symptoms including social, emotional, and cognitive deficits. While positive symptoms can often be managed through antipsychotic treatment, there are very few effective therapies for negative symptoms, which severely impair normal functioning. The mechanisms underlying schizophrenia are poorly understood. There are strong genetic and environmental contributions to schizophrenia, and diverse neurotransmitter systems and neural subtypes are altered in schizophrenic patients, including deficits in parvalbumin-positive fast-spiking cortical interneurons. Recently, a significant genetic association was found between the microRNA-206 gene and schizophrenia. microRNAs are small, noncoding RNAs that are critical regulators of gene expression. microRNAs are enriched in the nervous system, and have been increasingly implicated in neuronal function, dysfunction, and psychiatric disorders. We describe a novel line of conditional miR-206 knockout mice that exhibit schizophrenia-like behavioral deficits, including impaired pre-pulse inhibition and performance in a cognitive task, and increased anxiety-like behaviors. miR-206 is known to be enriched in cortical inhibitory parvalbumin-positive neurons and is predicted to target several genes critical for GABAergic function. We find that miniature IPSC frequency is decreased in the prefrontal cortex of miR-206 knockout mice, consistent with decreased GABAergic signaling. These data support a critical role for miR-206 in proper function of inhibitory cortical neurons as well as sensorimotor gating and normal expression of cognitive and anxiety-like behaviors. Thus, miR-206 may be a candidate for the development of novel schizophrenia therapeutics.

Disclosures: M.P. Heyer: None. **M. Ishikawa:** None. **G. Feng:** None. **P.J. Kenny:** None.

Poster

770. Psychosis: Animal Models

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Program#/Poster#: 770.06/D39

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: Deletion of slc6a7 which encodes PROT, the high-affinity sodium-dependent transporter for L-proline, results in multiple behavioural phenotypes relevant to psychiatric disorders

Authors: *D. C. HARRISON, K. BRACKENBOROUGH, J. ROBERTSON, M. HILL, P. GOETGHEBEUR, J. LAWRENCE, C. BENDER, J. DORAN, R. FRADLEY, S. NIZAMI, N. BRICE;
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Abstract: The amino acid L-proline has been proposed to act as a neuromodulator, or a neurotransmitter. In synaptosome experiments, it is released in response to calcium entry and several studies have shown alterations to glutamate-mediated post-synaptic potentials in response to L-proline. Additionally, there is a high affinity sodium dependent transporter specific for L-proline, PROT, found on pre-synaptic nerve termini. This is a member of the neurotransmitter transporter family which mediate re-uptake of neurotransmitters following synaptic action. We have generated a slc6a7 knockout mouse which lacks PROT. *In situ* hybridisation revealed a lack of mRNA for slc6a7 in all brain areas in KO mice, whereas WT mice expressed slc6a7 in cerebral cortex, thalamus, hippocampus and amygdala. Counterstaining with markers for glutamatergic and GABAergic neuronal types challenged the view that PROT is only found in glutamatergic neurons. Cortical, striatal and hippocampal synaptosomes prepared from slc6a7 KO mice had reduced uptake of radiolabelled L-proline compared with synaptosomes from WT mice. Slc6a7 KO mice were subjected to a battery of behavioural tests designed to detect phenotypes relevant to psychiatric disorders. KO mice showed enhanced cognitive performance in novel object recognition and spatial recognition tasks and an autoshaping test. In the elevated plus maze test, KO mice displayed increased anxiety compared to WT mice and in a tail suspension test the time spent immobile was reduced in KO mice. KO mice had a reduced hyperactivity response to the NMDA receptor antagonist MK-801, and reduced prepulse inhibition of the acoustic startle reflex. In a social interaction test there was no difference between WT and KO mice. Compared with other members of the neurotransmitter re-uptake family of transporters, PROT has received little attention as a putative drug target for psychiatric disorders, although inhibitors have been proposed as cognitive enhancers. These data suggest that the therapeutic potential for PROT inhibition is much broader and may encompass disorders such as schizophrenia, depression and anxiety.

Disclosures: **D.C. Harrison:** A. Employment/Salary (full or part-time):; Takeda. **K. Brackenborough:** A. Employment/Salary (full or part-time):; Takeda. **J. Robertson:** A.

Employment/Salary (full or part-time):; Takeda. **M. Hill:** A. Employment/Salary (full or part-time):; Takeda. **P. Goetghebeur:** A. Employment/Salary (full or part-time):; Takeda. **J. Lawrence:** A. Employment/Salary (full or part-time):; Takeda. **C. Bender:** A. Employment/Salary (full or part-time):; Takeda. **J. Doran:** A. Employment/Salary (full or part-time):; Takeda. **R. Fradley:** A. Employment/Salary (full or part-time):; Takeda. **S. Nizami:** A. Employment/Salary (full or part-time):; Takeda. **N. Brice:** A. Employment/Salary (full or part-time):; Takeda.

Poster

770. Psychosis: Animal Models

Location: Hall A

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Program#/Poster#: 770.07/D40

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: AMED-CREST, AMED

Title: Analysis of the mechanism underlying anxiety-like behavior observed in neuron-specific Dnmt1 knock-out mice

Authors: *A. KIMURA[1], H. NOGUCHI[1], M. OTSUKA I.[2,3], K. IGARASHI[2,3], T. IMAMURA[1], M. NAMIHIRA[4,3], K. NAKASHIMA[1,3];
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Abstract: Epigenetic modifications such as DNA methylation in the brain have become considered to be implicated in psychiatric disorders, since environmental factors, in addition to genetic factors, have appeared to be associated with such diseases. Recently, abnormal expression of DNA methyltransferase 1 (DNMT1) has been reported in the brains of bipolar disorder and schizophrenia patients. Missense mutations in DNMT1 were also suggested to contribute to the risk of schizophrenia. Thus, it is conceivable that the dysfunction of DNMT1 is one of the causal problems of psychiatric disorders. To reveal the relationship between the dysfunction of DNMT1 and psychiatric disorders, we generated neuron-specific Dnmt1 conditional knock-out (cKO) mice by crossing *Synapsin-Cre* and floxed *Dnmt1* mice. First we examined the expression of DNMT1 in the brains of *Dnmt1* cKO mice by immunohistochemistry, and found that neurons in dentate gyrus (DG) prominently lost DNMT1 expression. Next we performed behavioral analysis of Dnmt1 cKO mice and they showed anxiety-like behavior in the open field test. We also conducted microarray analysis by using cultured neurons from DG, in which Dnmt1 was knocked-down. Gene ontology (GO) analysis of

our microarray data revealed the enrichment of genes involved in voltage-gated calcium channel complex, voltage-gated potassium channel complex and dendritic formation. Furthermore, we compared our microarray data to the publicly available microarray data sets of hippocampus from bipolar disorder and schizophrenia patients, revealing that several genes in the above-mentioned GO terms are similarly up- or down-regulated. In addition, we performed sholl analysis of *in vitro* cultured neurons with Dnmt1 knockdown, and observed that the reduction of Dnmt1 expression increased the dendritic complexity. Taken together, these findings raise a possibility that the dysregulation of these gene expressions could be causes of the morphological change of neurons and the anxiety-like behavior observed in *Dnmt1* cKO mice.

Disclosures: **A. Kimura:** None. **H. Noguchi:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; CREST, JST. **M. Otsuka I.:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; CREST, JST. **K. Igarashi:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; CREST, JST. **T. Imamura:** None. **M. Namihira:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; CREST, JST. **K. Nakashima:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; CREST, JST.

Poster

770. Psychosis: Animal Models

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 770.08/D41

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: NIH Grant R01MH101102

Title: Abnormal hippocampal-mPFC connection in the KCNH2-3.1 transgenic mouse

Authors: *M. REN, G. CARR, Z. HU, Q. TIAN, T. M. HYDE, J. E. KLEINMAN, D. R. WEINBERGER, F. YANG;
The Lieber Inst. for Brain Develop., Baltimore, MD

Abstract: The KCNH2-1A potassium channel conducts delayed-rectifier potassium currents that have a rapid activation and relatively slow inactivation in deactivation kinetics. Our previous work has identified a novel primate isoform of KCNH2-1A channel, the KCNH2-3.1 potassium channel, in human brain associated with schizophrenia. Over-expression of KCNH2-3.1 in cultured cortical neurons alters repetitive spiking rates by causing the changes of the KCNH2-3.1 channel properties. However, the consequence of lifelong over-expression of KCNH2-3.1 to neuronal function in the intact brain remains unknown. We have created a transgenic mouse expressing the KCNH2-3.1 isoform, with KCNH2-3.1 mRNA constitutively over-expressed in frontal cortex and hippocampus similar to that of schizophrenic postmortem brain. Expression of the KCNH2-3.1 channel alters spiking rates in pyramidal neurons in layer V of medial prefrontal cortex (mPFC) in these mice, analogous to that described in primary neuronal culture studies, and with remarkable schizophrenia-like behavior deficits, including working memory and object location memory in these mice. It has been proposed that failure of functional integration and flow of information between hippocampus and mPFC results in cognitive deficits in schizophrenia patients. The possibility of functional impairments between hippocampus and mPFC as key pathophysiological mechanisms associated with schizophrenic phenotypes in KCNH2-3.1 mice has not been explored before. In this study, we have made an *in vitro* brain slice preparation to preserve the ventral hippocampal afferent fibers projecting to mPFC, which allows us to induce the hippocampal-prefrontal dependent monosynaptic response in the slices assessed by *in vitro* slice whole-cell patch recording. Our data show that there is significant impairment in basal synaptic inputs from the ventral hippocampus projecting to pyramidal neurons in the layer 5/6 of KCNH2-3.1 mice (10 weeks old) compared to those in wild-type (WT) mice of the same age. Interestingly, there is no significant difference in the hippocampal-mPFC connections between KCNH2-3.1 mice and WT mice in juvenile mice (2-3 weeks old). This result implies that KCNH2-3.1-caused selective impairments in neural connections between hippocampus and mPFC that do not appear in early postnatal development but require experiential and developmental time. These findings provide further insights into the precise alterations in hippocampal-mPFC connectivity observed in this schizophrenia-associated animal model, and could ultimately help elucidate the molecular and cellular basis underlying schizophrenia pathogenesis.

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Poster

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Program#/Poster#: 770.09/D42

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: Prepulse inhibition deficit correlates with forebrain Neuregulin-1 Type III mRNA overexpression in a novel transgenic mouse model for schizophrenia

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Abstract: Neuregulin-1 (NRG1) is a well-characterized risk gene for schizophrenia (SZ). Elevations in NRG1 protein and transcripts have been found in SZ with a recent study showing that the transcript for the Type III isoform of NRG1 (NRG1-III) is overexpressed in the forebrain of SZ patients that carry a risk haplotype for the NRG1 gene. In light of this, a mouse overexpressing Nrg1-III specifically in the forebrain was created in order to assess how Nrg1-III overexpression might cause or contribute to SZ-related deficits. We hypothesised that Nrg1-III overexpressing transgenic mice would show behavioural deficits relevant to SZ such as prepulse inhibition (PPI) deficits as well as social and cognitive impairments. Male adult mice (10 Nrg1-III transgenic and 10 WT-like) between the ages of 30 to 34 weeks underwent a standardized behavioural test battery and brains were collected post testing to analyse mRNA expression levels of Neuregulin-1 Type III as well as for three housekeeper genes in the prefrontal cortex (PFC) using qPCR. Nrg1-III tg mice had an increase in normalized Nrg1-III mRNA expression in the PFC ($t=8.55$, $p<0.0001$, $n=12$-14) and displayed impaired learning of a fear-eliciting context ($F=3.81$, $p=0.024$, $n=7$-10), spent less time interacting with a novel social opponent ($t=2.789$, $p=0.044$, $n=10$) and had a deficiency in prepulse inhibition (140.2%, $F=11.281$, $p=0.004$, $n=9$-10) that negatively correlated with the normalized Nrg1 Type III mRNA expression in the PFC of mice of both genotypes [$r=-0.54$, $p=0.0261$]. Our findings confirm that the Nrg1-III tg mouse has a robust overexpression of Nrg1-III mRNA in forebrain (similar to that found in the disease state of a subset of SZ patients) and that this overexpression causes PPI deficits, social recognition and cognitive impairment. In addition, PPI performance may be reflected by Nrg1-III levels in the forebrain where increasing levels of Nrg1-III predicts worse PPI performance. Together, these results indicate that this novel transgenic mouse model has construct and face validity for SZ and provide evidence that an overexpression of Nrg1-III may contribute to the symptomatology of SZ.

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Poster

770. Psychosis: Animal Models

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Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: Brain Research Foundation (SCD)

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T32MH020065 (MJR)

Title: Behavioral screen in DLGAP1 mutant mice for phenotypes relevant to Obsessive Compulsive Disorder and Schizophrenia-like behaviors

Authors: ***M. RAMAKER**[1], E. V. HO[1], J. A. KNOWLES[2], N. H. KOMIYAMA[3], S. G. N. GRANT[3], S. C. DULAWA[1];
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Abstract: Introduction: Recent Genome Wide Association Studies (GWAS) and de novo copy number variant (CNV) analyses have identified several genes relevant to psychiatric illnesses such as Obsessive Compulsive Disorder (OCD) and schizophrenia. One gene identified to be a susceptibility gene for both disorders is DLGAP1, which codes for a scaffolding protein present in the post-synaptic density of glutamatergic neurons. The present study aimed to screen DLGAP1 mutant mice for phenotypes relevant to OCD or schizophrenia-related behaviors. Methods: Male and female DLGAP1 knockout (KO), heterozygote (HT), and wild-type (WT) mice were evaluated in the following behavioral tests: open field, dig, splash, social interaction, nestlet building, prepulse inhibition, and forced swim. Fos mRNA was measured in orbital frontal cortex, caudate/putamen, and cerebellum. Results: Genotypic differences were observed in the dig, splash, and social interaction tests. Specifically, DLGAP1 KO males showed reductions in grooming in the splash test and exhibited reductions in number of digging bouts

and increases in latency to dig in the dig test. KO and HT males showed reduced sociability in horizontal measures in the social interaction test and there was a reduction across genders for vertical measures of sociability in the social interaction test. There were no genetic differences in: body weight, open field measures (horizontal, center time, or vertical activity, or spatial d) nestlet building, prepulse inhibition, or the forced swim test. There were also no effects of genotype for Fos expression in orbital frontal cortex, caudate/putamen, or cerebellum. Conclusions: DLGAP1 mutant mice showed alterations in social, anhedonic, and exploratory measures, which display relevance to schizophrenia-like phenotypes. On the other hand, this behavioral screen did not find alterations in behaviors relevant to OCD-like phenotypes. These data suggest that the DLGAP1 gene may contribute to some of the behavioral deficits involved in schizophrenia-like behaviors. Future studies examining whether drugs used to treat schizophrenia would be effective in reversing abnormal behaviors may further clarify the contribution of the DLGAP1 gene to phenotypes related to schizophrenia.

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Poster

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Topic: C.15. Schizophrenia and Bi-polar Disorder

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We thank Prof. Penninger for the gift of the mice

Title: Assessment of minocycline upon cognitive performance in mice haploinsufficient for the schizophrenia risk gene Mitogen-Activated Protein Kinase 7 (Map2k7)

Authors: *J. A. PRATT[1], B. J. MORRIS[2], R. L. OPENSHAW[2];
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Abstract: Recent advances in understanding the genetic architecture of schizophrenia provide an opportunity to investigate the neurobiological role of risk variants upon neurotransmitter systems, brain networks and behaviour in rodent models and to assess their potential for drug discovery. Here we investigate mice haploinsufficient for Map2k7 (Map2k7+/-), a gene

functionally associated with schizophrenia [Winchester et. al., 2012 Human Molecular Genetics. 21: 4910-4921], in two translationally relevant cognitive tasks and in which schizophrenia patients show deficits: the 5-choice serial reaction time task (5-CSRTT) for attention and inhibitory control and the paired associates learning (PAL) task for object-in-place memory. Performance was also assessed before and after administration of minocycline, a tetracycline antibiotic currently undergoing clinical trials in schizophrenia. The 5-CSRTT requires mice to attend to responding, via nose poke, to a brief light stimulus in one of five spatial locations over ~100 trials and PAL necessitates mice to learn and report the correct location of three different images on a touchscreen. Eight- ten week old mice were trained on either the 5-CSRTT in a 9-hole operant chamber (Med Associates) (16 Map2k7(+/-) (9 male), 15 wild-type littermates (WT; 8 male)) or PAL in a touchscreen chamber (Campden Instruments) (10 Map2k7(+/-) (5 male), 10 WT (5 male)) until their performance stabilised. All mice were then given minocycline in their drinking water for 7 days (86mg/kg/day on average received) and re-tested on the 5-CSRTT/PAL on days 4 and 7. Data was analysed by repeated measures ANOVA with session as the within subjects factor and genotype as the between subjects factor. In the 5-CSRTT, while accuracy was unimpaired, Map2k7+/- mice missed significantly more target stimuli than WTs ($F(1,154)=42.36$; $p<0.001$) and all mice showed improvement in % missed after minocycline treatment, from Map2k7+/-: 7.8±3.1% to 11.8±1.7%; WT: 12.6±1.3% to 10.1±1.7% ($F(2,58)=2.95$;$p=0.06$). Map2k7+/- mice were also impaired in the PAL task: they made less correct responses ($p<0.001$; $f(1,72)=17.84$), and required more correction trials ($p=0.047$; $F(1,72)=4.08$) than WT littermates. Overall, Map2k7+/- mice display deficits in the 5-CSRTT and the PAL task and some of these deficits showed signs of improvement with administration of minocycline. These results support Map2k7+/- mice being an informative and translatable model of some aspects of schizophrenia, with potential for aiding future development of improved treatments.

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Poster

770. Psychosis: Animal Models

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Topic: C.15. Schizophrenia and Bi-polar Disorder

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Avina Foundation

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Alamaya Foundation

Title: Interaction between Redox dysregulation and Neuroinflammation during early development could lead to PVI circuitry impairments in adulthood: relevance for schizophrenia

Authors: *D. DWIR[1], J.-H. CABUNGCAL[1], P. STEULLET[1], R. TIROUVANZIAM[2], K. Q. DO[1];
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Abstract: Schizophrenia (SZ) is a major psychiatric disease which involves both genetic and environmental factors. Glutathione (GSH), a main cellular antioxidant and redox regulator, is decreased in CSF and brain of patients. The key GSH synthesizing genes present polymorphisms associated with the disease. Thus, a redox dysregulation during neurodevelopment may be a critical risk factor for SZ when genetic vulnerability for redox dysregulation and environmental stressors generating oxidative stress converge. Moreover, oxidative stress is known to induce inflammation. Anomalies in peripheral immune cells as well as dysregulation of immune-related genes have been reported in SZ. The interaction between both processes occurring at critical period during brain development may affect neurons vulnerable to elevated oxidative insults, such as parvalbumin-expressing interneurons (PVI), which circuit is impaired in post-mortem SZ brain. Mature cortical PVI are usually surrounded by a perineuronal net (PNN), which might be degraded by matrix metalloproteinases (MMPs), induced in pro-inflammatory condition and activated by oxidative stress. We used a transgenic mouse model with GSH deficit (GCLM -/-) that shows SZ related phenotype, to investigate the interaction between oxidative stress and neuroinflammation in early development, to account for the aversive effect on PVI/PNN circuitry in adult.We compared PVI, PNN and microglia level in the anterior cingulate cortex (ACC) of GCLM-/- and WT mice at peripuberty and in adulthood. In addition, mice were treated with a dopamine reuptake inhibitor (GBR) to pharmacologically induce additional oxidative insult from postnatal days (P) 10 to 20. GBR treatment in young mice led to a decreased PVI+ and PV-PNN+-IR, increased oxidative stress level and microglia activation in adult GCLM-/-, showing the tight interaction between the redox and inflammatory state. Microglia activation was more pronounced at peripubertal stage compared to adulthood, suggesting a stage specific vulnerability in GCLM-/-. We explored the role of RAGE, which is activated by ligands produced by oxidative stress, and found increased RAGE shedding in neurons as well as increased MMP9-IR in GCLM-/- at P40. Interestingly, a specific inhibitor of MMP9 prevented RAGE shedding and microglia activation in the ACC of P40 GCLM-/-, demonstrating the involvement of MMP9 and suggesting that this treatment could also limit oxidative stress and

PVI/PNN deficit. We propose that an interaction between redox dysregulation and pro-inflammatory condition via RAGE/MMP9 in early development is a potential trigger of structural and morphological impairments in adult.

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Poster

770. Psychosis: Animal Models

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Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: Effects of post-weaning isolation and the Nurr1-null heterozygous genotype on behavior

Authors: *J. B. EELLS, S. X. GUO-ROSS, T. E. BRANYAN;
Mississippi St Univ., Mississippi State, MS

Abstract: The NR4A2 gene encodes the protein Nurr1, a nuclear receptor similar to thyroid/steroid hormone receptors, that is essential for the differentiation, development and maintenance of mesencephalic dopamine neurons. Specifically, the Nurr1 null-heterozygous (+/-) genotype results in reduced nucleus accubens dopamine tissue levels and elevated open field activity. The combination of the +/- genotype and post-weaning isolation results in disrupted prepulse inhibition, elevated amphetamine stimulated dopamine release and attenuated Nurr1 protein in dopamine neurons. To investigate further the interactions between the Nurr1 +/- genoptype and post-weaning isolation, male +/+ and +/- mice were raised in either groups or isolation at weaning and tested on open field activity during their light phase (between 0800-1000) then 3 weeks later tested again during the dark phase (between 2000-2200). Analysis of open field activity found that the +/- mice were significantly more active in an open field than the +/+ mice. Isolation had no significant effect on open field activity in the light phase. However, testing in the dark phase resulted in a trend toward elevated activity of the isolated +/- mice with an exacerbated difference between isolated +/+ and +/- mice. The +/- genotype and isolation both resulted in a reduction in body weight. Data on body weight and open field activity suggest that, although there is a relationship between activity and body weight, reduced body weight is not always associated with elevated open field activity as the isolated +/+ mice had a similar average body weight as the group raised +/- mice, although these groups had significantly different activity. These data demonstrate an interaction between the +/- genotype and isolation

on open field activity during the dark phase which suggests that these treatments could disrupt circadian rhythms and potentially alter the temporal regulation of dopamine neurotransmission.

Disclosures: **J.B. Eells:** None. **S.X. Guo-Ross:** None. **T.E. Branyan:** None.

Poster

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Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: *In vivo* application of CRISPR/Cas9 for studying Akt/Gsk3 signalling in regulation of mood

Authors: *J. KHLGHATYAN, S. CHAMBERLAND, K. TOTH, J. M. BEAULIEU; CRIUMSQ, Laval Univ., Quebec, QC, Canada

Abstract: Background. Neuropsychiatric disorders such as bipolar disorders, depression and schizophrenia represent a major public health problem, and a heavy burden for patients and their relatives. Drugs (such as mood stabilizers) used for management of these diseases shown to exert their effect partially by acting on Akt/Gsk3 pathway downstream of dopamine (DA) receptors. Moreover, this pathway is responsible for regulation of DA related behaviors. Ultimately, many schizophrenia risk genes encode proteins which either comprise or converge on this pathway. Few studies show that regulation of distinct behaviors by members of Akt/Gsk3 pathway may be brain region dependant. Therefore, more studies are needed to expand our knowledge on network specific regulation of behaviors by Akt/Gsk3 pathway. Additionally cell type specific involvement of Akt/Gsk3 signaling in regulation of behaviors remains elusive. Aim. To study the region and cell type specific role of Akt/Gsk3 pathway in regulation of behaviors. Results. Here we used the CRISPR/Cas9 technology to knockout Gsk3 gene in the mouse brain. First, gRNAs against Gsk3 were designed and validated *in vitro* by the Surveyor assay and western blot. For *in vivo* delivery, a dual viral system was implemented. One AAV viral vector was made containing the most active Gsk3 guide along with the fluorescent reporter (SpGuide6) while the Cas9 nuclease was part of second AAV viral vector (SpCas9). AAV5 viral particles were prepared and co-injected into the mouse brain. 2-3 weeks later, brains were dissected and *in vivo* Gsk3 knockout was validated by immunostaining. Moreover, functional consequences of Gsk3 knockout in particular networks of brain were assessed. Particularly knockout of Gsk3 gene in prefrontal cortex showed an anxiolitic effect in mice. Future directions. To understand the role of Akt/Gsk3 signalling in D2 neurons in particular networks of the brain, Gsk3 knockout will be

achieved in those neurons. For this reason conditional Cas9 knockin mice are crossed with D2Cre mice and expression of Cas9 in D2 neurons is observed. Upon delivery of SpGuide6 to different brain regions of D2CreCas9 mice, biochemical, functional and behavioral characterization will elucidate the role of Akt/Gsk3 cascade in D2 neurons in particular networks of the mouse brain.

Disclosures: J. Khlghatyan: None. **S. Chamberland:** None. **K. Toth:** None. **J.M. Beaulieu:** None.

Poster

770. Psychosis: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 770.15/D48

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: Role of GABAA receptor α1 subunit in ventral striatum medium spine neurons of erbb4-mutant mice

Authors: *H. GENG[1], X. LI[2];
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Abstract: Striatum is responsible for voluntary movements and cognitive functions and its dysfunction may lead to neuropsychiatric diseases. In this study, we observed that erbb4, a schizophrenia risk gene, has densely expressed in striatum. We found the expression of GABAA receptor alpha 1 subunit was significantly increased after knockout of ErbB4 in striatum; and the GABAergic transmissions on medium spiny neurons were also increased. Furthermore, we observed schizophrenia-like behaviors including hyperactivity and impaired social novelty recognition in these knockout mice. Intriguingly, these abnormalities were rescued by interfering with the expression of GABAA receptor alpha 1 subunit in ventral rather than dorsal striatum. These results indicates that ErbB4 is essential for GABAergic synaptic formation in ventral striatum and provides a new perspective for the understanding the role of ErbB4 and GABAergic synapses in the pathological process of neurodevelopment disorders.

Disclosures: H. Geng: None. **X. Li:** None.

Poster

770. Psychosis: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 770.16/E1

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: Dopamine D3 receptor antagonism rescues dopamine transporter knockdown-induced deficit in sensorimotor gating and cognition

Authors: *P.-K. CHANG;
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Abstract: Long-term stimulation in dopaminergic signaling is thought to underlie the pathophysiology of a number of psychiatric disorders, such as psychosis, mania and attention-deficit/hyperactivity disorder (ADHD). These conditions are associated with cognitive deficits such as disturbances in attention processes as well as learning and memory, suggesting that persistent changes in dopaminergic signaling may alter neural mechanisms and lead to disease progress. Of central dopamine system, dopamine D3 receptors have a pre- and postsynaptic localization in brain stem nuclei, limbic parts of the striatum, and cortex. Their widespread influence on dopamine release, function, and on several other neurotransmitter systems makes them an attractive target for therapeutic intervention. So far, all clinically used antipsychotics are not D2-selective but also have affinity towards D3 receptors. On the other hand, dopamine transporter knockdown (DAT-KD) mice exhibit a persistent 70% increase in extracellular dopamine levels than wild-type mice, hence has been widely used as a mania model. In this study, we found DAT-KD mice exhibited a loss in pre-pulse inhibition (PPI) and object recognition tests. However, these functional loss could be rescued by acute exposure of D3 selective antagonist, FAUC365. Next, we compared the behavioral outcome and biochemical phenotype between DAT-KD and D3/DAT double mutants to determine the role of D3 receptor on psychosis. Both mice exhibited hyper-locomotor activity and enhanced stereotypy. Accordingly, DAT-KD exhibited a loss in PPI and object recognition test, but D3/DAT double mutant mice preserved these functions. Overall, the present data implicate dopamine D3 receptors participate a functional role in sensorimotor gating and cognition.

Disclosures: P. Chang: None.

Poster

770. Psychosis: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 770.17/E2

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: SLC10A4 knockout mice show abnormal event-related potentials in response to an auditory paired-clicks gating test: implications for psychiatric disorders

Authors: *K. E. LEAO[1], M. M. HILSCHER[1], R. N. LEAO[1], H. PETTERSSON[2], M. BLUNDER[1], K. KULLANDER[2];
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Abstract: Slc10A4 is a vesicular monoaminergic and cholinergic associated transporter, and SLC10A4-knockouts (ko) show indications of a greater vulnerability to psycomimetic drugs making them a potential animal model for psychiatric diseases. Here, we use low dose ketamine (5mg/kg and 20mg/kg) to challenge animals and measure alterations in auditory event-related potential profiles to elucidate temporal components that could serve as markers for psychiatric disorders. Human electro-encephalogram (EEG) studies indicate an impaired sensory filtering capacity of auditory paired-clicks in schizophrenia and/or bipolar disorders. These event-related potentials seen in human EEGs in response to paired-clicks have distinct temporal peaks and can be semi-replicated by intrahippocampal electrode recordings in rats and mice. We compare auditory event-related potentials in freely moving mice chronically implanted with 16 channel intrahippocampal electrodes in SLC10A4 ko mice and control littermates. We found that intrahippocampal signal polarity and temporal acuity was strongly influenced by electrode placement within the layers of the hippocampus, which may explain the lack of consistency in previous studies that used single recording electrodes. We found a 'typical' response, with smaller amplitude to the second click, only in certain distinct layers for both controls and ko's following saline injections. In general, SLC10A4-ko's displayed a more complex waveform with extra peaks compared to control littermates. Low dose ketamine mildly affected event-related potentials in control animals but strongly alter the waveform in ko mice. Preliminary results from pre-pulse inhibition show SLC10A4 ko's to startle even following a low sound level prepulse, whereas controls do not. Taken together, these results indicate that SLC10A4-ko animals, with alterations in modulatory neurotransmission systems, are more sensitive to low dose ketamine as well as to startle tests than controls. Our results also indicate a role of Slc10A4 in psychiatric disorders and suggest that this transporter may be a target for psychotherapy.

Disclosures: K.E. Leao: None. **M.M. Hilscher:** None. **R.N. Leao:** None. **H. Pettersson:** None. **M. Blunder:** None. **K. Kullander:** None.

Poster

770. Psychosis: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 770.18/E3

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: Wellcome Trust PhD Studentship

Title: NMDAR-knockout in parvalbumin interneurons sensitises not protects mice from the effects of MK801

Authors: *A. BYGRAVE, S. MASIULIS, D. BANNERMAN, D. KAETZEL;
Univ. of Oxford, Oxford, United Kingdom

Abstract: The glutamate hypothesis of schizophrenia suggests that N-methyl D-aspartate receptor (NMDAR) hypofunction is central to the disease. In particular, a functional deficit of NMDA receptors (NMDARs) on parvalbumin (PV) positive interneurons has been proposed to be at the core of the pathology of schizophrenia. The non-competitive NMDAR antagonist Dizocilpine (MK801) leads to a paradoxical increase in cortical activity via dis-inhibition of pyramidal neurons because fast spiking interneurons appear more sensitive to the action of NMDAR antagonists. In two previous studies, genetically modified mice lacking NMDARs selectively on PV interneurons (PV-NR1 KO) were reported to be protected from the hyperlocomotor inducing effects of MK801, identifying PV neurons as an important target of the drug. In this study we tested the hypothesis that PV-NR1 KO mice are protected from the hyperactivity and cognitive impairments induced by MK801. Surprisingly, and in contrast to previous studies, we found that PV-NR1 KO mice were sensitised, not protected, to MK801 challenge. PV-NR1 KO mice did not show hyperactivity in response to MK801 challenge but their reduced locomotion resulted from catalepsy, not ineffectiveness of the drug. Furthermore, MK801 impaired performance in a test of working memory at lower doses in PV-NR1 KO than in control mice. These findings challenge the theory that psychotropic effects of MK801 are primarily mediated via PV interneurons.

Disclosures: **A. Bygrave:** None. **S. Masiulis:** None. **D. Bannerman:** None. **D. Kaetzel:** None.

Poster

770. Psychosis: Animal Models

Location: Hall A

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Program#/Poster#: 770.19/E4

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: NSC 102-2628-B-002-014-MY3

Title: Amphetamine-induced locomotive activity in heterozygous Disc1 mutant mice

Authors: *C.-C. LAI[1], L.-J. LEE[1,2,3];
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Abstract: Disrupted-in-Schizophrenia-1 (DISC1) is a susceptibility gene for several psychiatric illnesses, such as autism and schizophrenia. To study the pathogenesis of these disorders, various Disc1 mutant mouse models were established. In our group, Disc1 mutant mice were generated by introducing the 129S6/SvEv 25-bp deletion Disc1 variants into the C57BL/6J strain. In this study, a battery of behavioral tasks was conducted to evaluate the behavioral phenotypes and cognitive function in the heterozygous Disc1 mutant (Het) mice. In open field test, novel object recognition test, Y-maze test, and prepulse inhibition test, no significant differences were noted between wildtype (WT) and Het mice. However, after received an intraperitoneal injection of amphetamine (5 mg/kg), compared with WT mice, greater locomotive activity was noticed in Het mice. Our results suggested that Disc1 deficit in one allele dose not significantly affect basic behavior and cognition in mice. However, lacking one WT Disc1 allele dose produce greater reaction following the challenge of psychostimulant such as amphetamine. These phenotypes in Het mice resemble the condition in patients with schizophrenia. Our results also suggest a role of dopaminergic system dysfunction in the pathogenesis of schizophrenia.

Disclosures: C. Lai: None. **L. Lee:** None.

Poster

770. Psychosis: Animal Models

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Program#/Poster#: 770.20/E5

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: P50MH086404

R01MH093672

Title: Increased striatal dopamine d2 receptor activity is associated with increases in population activity of substantia nigra dopamine neurons

Authors: *M. O. CHOHAN[1,3], M. CAZORLA[5], H. MOORE[1,3], C. KELLENDONK[2,3,4];
[1]Integrative Neurosci., [2]Mol. Therapeut., New York State Psychiatric Inst., New York, NY;
[3]Psychiatry, [4]Pharmacol., Columbia Univ., New York, NY; [5]Inst. Curie, Paris, France

Abstract: Midbrain dopamine (DA) neurons are important modulators of striatally dependent behaviors. In schizophrenia (SCZ), there is excessive striatal DA d2 receptor (D2R) transmission, particularly in the associative caudate. While most antipsychotic drugs in use block D2Rs, the mechanisms by which therapeutic benefits are achieved remain unclear. One compelling hypothesis of particular relevance to antipsychotic drug action is that D2R blockade in the striatum induces depolarization block in DA neurons lowering their population activity. We recently identified a critical role for D2Rs in the regulation of basal ganglia functional connectivity: D2Rs chronically regulate density of axon collaterals bridging the 'direct' striatonigral and 'indirect' striatopallidal pathways in the globus pallidus (GP) by modulating medium spiny neuron (MSN) excitability. Modeling increased striatal D2R function in a mouse model, we found that in mice overexpressing striatal D2Rs (D2ROE mice), increased D2R expression is associated with increased inhibition of GP and a disruption of direct pathway mediated locomotor behavior. In the present study we decided to determine whether increased postsynaptic D2R function has an impact on the presynaptic DA neuron activity in the substantia nigra, a region known to send dense projections to the associative caudate. Using single unit *in vivo* extracellular recording methods in anesthetized mice, we recorded from nigrostraital DA neurons before and after switching off the transgene in adult animals. We found an increase in the number spontaneously active DA neurons in mice with increased D2R function. The increased population activity was recovered following switching off the transgene in adulthood. However, increased D2R function did not seem to affect basal firing frequency and burst parameters (percent spikes fired in bursts and burst rate) of DA neurons. By modulating GP neuronal activity, bridging collaterals may regulate DA neuron population activity - disinhibiting nigrostriatal DA neurons in D2ROE mice that have increased bridging collaterals in the GP. Since chronic haloperidol treatment decreases bridging collaterals in the mouse, we asked whether this is associated with a decrease in population activity. Wild-type mice were treated with 1 mg/kg haloperidol using minipumps for 2 weeks. We found a decrease in population activity of DA neurons while firing frequency and burst parameters remained unchanged. Our data suggest bi-directional regulation of DA population activity by striatal D2Rs, which could be a consequence of D2R-mediated anatomical changes in the striatal output pathways.

Disclosures: **M.O. Chohan:** None. **M. Cazorla:** None. **H. Moore:** None. **C. Kellendonk:** None.

Poster

770. Psychosis: Animal Models

Location: Hall A

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Program#/Poster#: 770.21/E6

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: T32 MH 76690-6 A1

Title: Sexually dimorphic effects in a double-risk model of psychosis

Authors: *D. SCOTT, C. TAMMINGA;
Psychiatry, UT Southwestern, Dallas, TX

Abstract: Schizophrenia is a serious mental illness affecting approximately 1% of the world's population. It is characterized by positive symptoms, also referred to as psychosis, as well as negative symptoms and cognitive dysfunction. Although many of the negative and cognitive symptoms are easily modeled in experimental animals, thus giving insight into the basic mechanisms underlying these specific symptoms, animal models of the positive symptoms have been weak in providing a valid representation of psychosis. In order to better model the positive symptoms of schizophrenia, we utilized a double-risk model combining genetic risk (with mice carrying a dominant negative form of the schizophrenia-associated gene DISC1) with environmental stress (maternal deprivation), which is known to increase the risk of developing schizophrenia. We conceptualize psychosis as a memory disorder, induced by hippocampal hyperactivity as indicated by human imaging and postmortem tissue studies. We hypothesize that environmental risks will increase the severity of tissue pathology accompanying the genetic profile for schizophrenia, which reveals itself in behavioral deficits relevant to psychosis and memory, as well as increased activity in the CA3 subfield of the hippocampus. To address this hypothesis, we exposed wild-type (WT) and DISC1-deficient (TG) mice to either a mild (one hour daily) or severe (three hours daily) maternal deprivation stress from P2 to P14. Once these animals reached adulthood, they were tested in a battery of behavioral experiments, and examined for signs of increased hippocampal neuronal activity. Results suggest maternal deprivation and DISC1 deficiency selectively decrease fear conditioning in female, but not male mice, though the effects are not additive, suggesting these two risk factors may share a common biological mechanism for schizophrenia. Furthermore male mice display hyperactivity only when exposed to a mild, but not severe, maternal deprivation stress, with TG mice showing no difference from WT mice. Studies are underway examining neuronal activity in the hippocampal subfields by way of quantifying c-fos expression. Overall, these results suggest a distinct sex difference in the susceptibility of animals to both the environmental as well as genetic risk factors contributing to psychosis, and further research is needed to determine how these correlate

with hippocampal hyperactivity. The overall development of a strong inference animal model of psychosis would satisfy a high medical need in schizophrenia research.

Disclosures: D. Scott: None. **C. Tamminga:** None.

Poster

770. Psychosis: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 770.22/E7

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: Socio-communicative deficits in serine racemase knockout mice

Authors: *A. E. YOUNG[1], M. T. PISANSKY[2], J. C. GEWIRTZ[3];
[2]Neurosci., [3]Psychology, [1]Univ. of Minnesota- Twin Cities, Minneapolis, MN

Abstract: Evidence suggests that reduced function of glutamatergic NMDA receptors contributes to the pathophysiology of schizophrenia. NMDA receptor function is modified endogenously via the allosteric modulator D-serine, which is synthesized by the enzyme serine racemase. Schizophrenia is characterized in part by deficits in social-communicative, emotional, and cognitive domains. To examine the effects of serine racemase dysfunction in each of these domains, we subjected mice harboring a deletion of this gene to a number of relevant behavioral tests. Juvenile serine racemase knockout mice exhibited reduced social interactions and emissions of ultrasonic vocalizations. Consistent with previous findings, adults showed deficits in prepulse inhibition, a measure of sensorimotor gating. Lastly, we are conducting experiments to assess socially transmitted fear behavior of serine racemase knockout mice as a measurement of socio-emotional cognition. These results suggest reduced glutamatergic neurotransmission via the NMDA receptor gives rise to abnormal behaviors in the socio-communicative domain that parallel some of the negative symptoms associated with schizophrenia.

Disclosures: A.E. Young: None. **M.T. Pisansky:** None. **J.C. Gewirtz:** None.

Poster

770. Psychosis: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 770.23/E8

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: Mouse brain expression and function of Regulator of G protein Signaling-12 (RGS12) in sensorimotor gating and locomotive behaviors

Authors: *J. D. GROSS, V. SETOLA, K. A. WIX, D. P. SIDEROVSKI;
Physiol. & Pharmacol., West Virginia Univ. Sch. of Med., Morgantown, WV

Abstract: "Regulator of G protein Signaling" (RGS) proteins accelerate the rate of GTP hydrolysis by heterotrimeric G protein alpha subunits, thereby inhibiting G protein-coupled receptor signaling. Regulator of G protein signaling-12 (RGS12) exerts this canonical GTPase-accelerating activity via its central RGS domain and also performs other signal regulatory functions via a complex multidomain architecture composed of an N-terminal PDZ and phosphotyrosine binding (PTB) domain, two Ras-binding domains (RBDs), and a C-terminal GoLoco motif. Independent studies that performed exome sequencing of schizophrenic (SCZ) and schizoaffective (SZA) patients and their parents have identified de novo Rgs12 variants within two affected probands (Xu et al., 2011 and Guipponi et al., 2014), both of which are predicted to be non-synonymous missense mutations. Our lab has now shown that RGS12 is expressed in the mouse CNS within deep lateral cortical layers, striatum, hippocampus, and claustrum -- regions associated with the pathogenesis of SCZ. Furthermore, we recently found that Rgs12-deficient mice exhibit altered responsiveness in prepulse inhibition of acoustic startle and display altered locomotor responses to several psychotomimetic and psychostimulant drugs. Further investigation into the CNS function of RGS12 may illuminate novel therapeutic approaches for treating psychiatric diseases such as SCZ.

Disclosures: **J.D. Gross:** None. **V. Setola:** None. **K.A. Wix:** None. **D.P. Siderovski:** None.

Poster

770. Psychosis: Animal Models

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Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: NIH Grant AG047669

CMG Training Grant

Aginsky Fellowship

Title: Neuregulin 1 and cholinergic control of behavior in mice

Authors: *L. SERVILIO[1,2], K.-F. LEE[2];
[1]UC San Diego, San Diego, CA; [2]Salk Inst., La Jolla, CA

Abstract: Neuregulin 1 (Nrg1) is a genetic risk factor of schizophrenia and has been shown to play many important roles in the central and peripheral nervous systems. While Nrg1 is widely studied, its function in the cholinergic circuitry of the brain remains largely unknown. Changes in cholinergic activity can have widespread effects throughout the brain, thus it is important to understand how Nrg1 regulates this circuitry. We used mice with a conditional knockout of Nrg1 in cholinergic neurons to investigate resulting anatomical and behavioral changes. We found that in wild type mice Nrg1 is expressed in cholinergic projection neurons of basal forebrain and the brainstem, where it forms clusters around the soma and proximal dendrites of these cells. Nrg1 is often localized to synapses where presynaptic neurons are also cholinergic. Further, Nrg1 influences the localization of muscarinic receptors at these synapses. In the conditional knockout mice, Nrg1 clustering was abolished and M2 muscarinic receptors were distributed more evenly around the cell body. The conditional knockout mice exhibited several interesting behavioral phenotypes suggesting disruption of cholinergic activity, including decreased prepulse inhibition and increased vocalizations. This evidence suggests that Nrg1 plays an important role in the cholinergic circuitry of the mouse brain, and disruption of this gene solely in cholinergic pathways can lead to marked behavioral changes with potential implications for neuropsychiatric diseases.

Disclosures: L. Servilio: None. **K. Lee:** None.

Poster

770. Psychosis: Animal Models

Location: Hall A

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Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: MH073991

MH086075

Title: Mitochondrial dysfunction in humanized DISC1-Boymaw mice

Authors: *K. K. HIGA, B. JI, M. A. GEYER, X. ZHOU;
Psychiatry, UC San Diego, La Jolla, CA

Abstract: The Disrupted in Schizophrenia 1 (DISC1) translocation, a mutation found across several generations of a large Scottish family, is the most promising causal genetic lesion for schizophrenia, bipolar disorder, major depression, and other psychiatric disorders. Two fusion genes_DB7 and BD13, from DISC1 on chromosome 1 and Boymaw on chromosome 11_are generated by the translocation. We found that expression the DB7 fusion gene in cultured cells inhibits oxidoreductase activity, rRNA expression, and protein translation. In addition, the DB7 protein colocalizes with mitochondria, where it abolishes mitochondrial membrane potential. To study the effects of the translocation *in vivo*, we developed humanized "DISC1-Boymaw" mice that express both human fusion genes. In addition to reduced rRNA synthesis and protein expression, the heterozygous (HET) DISC1-Boymaw mice exhibit exaggerated locomotor responses to ketamine, as well as mild depressive-like behaviors, not observed in their wildtype (WT) littermates. We hypothesize that expression of the DB7 protein causes mitochondrial dysfunction, which leads to impaired ATP production and an increased reliance on glycolysis as a means of energy production, both of which have been observed in patients with psychiatric disorders. Consistent with this hypothesis, we have found that activation of AMPK, an energy sensor that is activated due to high AMP/ATP ratio (i.e., low energy), is increased in HET mice. Furthermore, we have found that the respiratory exchange ratio (volume of CO2 produced / volume of O2 consumed) is higher in HET mice than in WT mice, suggesting a bioenergetic shift from oxidative phosphorylation to glycolysis. Mitochondrial dysfunction may disrupt the AMPK-mTOR protein pathway, leading to the observed inhibition of protein translation. Reduced protein translation can affect neurotransmission and plasticity necessary for normal brain development and function. Understanding the mechanisms and consequences of mitochondrial dysfunction on ATP production and protein translation in the DISC1-Boymaw mice may help elucidate the molecular pathways for the pathogenesis of schizophrenia, bipolar disorder, and major depression in the Scottish family and the general population of psychiatric patients.

Disclosures: **K.K. Higa:** None. **B. Ji:** None. **M.A. Geyer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); San Diego Instruments. F. Consulting Fees (e.g., advisory boards); Abbott, Dart, Lundbeck, Neurocrine, Omeros, Otsuka, Sunovion. **X. Zhou:** None.

Poster

770. Psychosis: Animal Models

Location: Hall A

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Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: University of Sydney Bridging Grant

Bosch Translational Grant-in-Aid to JCA

Title: Partial genetic deletion of neuregulin 1 modulates the effects of chronic stress on dendritic morphology in adolescent mice

Authors: *D. J. CLARKE[1,2,3,4], T. CHOHAN[2,4,3], M. S. KASSEM[2], S. Y. FOK,[2], M. R. BENNETT[2], J. C. ARNOLD[4,2,3];
[1]Pharmacol., The Univ. of Sydney, Werrington Downs, Australia; [2]Brain and Mind Res. Inst., Sydney, Australia; [3]Bosch Inst., Sydney, Australia; [4]Pharmacol., Univ. of Sydney, Sydney, Australia

Abstract: Neuregulin 1 (Nrg1) is a neurotrophic factor and a schizophrenia susceptibility gene. Dendritic spine atrophy has been observed in the schizophrenia brain. Chronic restraint stress promotes alterations in dendritic morphology including a decrease in dendritic spine density in the medial prefrontal cortex and the hippocampus, and an increase in dendritic spine density in the basolateral amygdala. On this background, we aimed to examine whether partial genetic deletion of Nrg1 modulated stress-induced changes in dendritic morphology. Adolescent wild-type (WT) and neuregulin heterozygous (Nrg1 HET) mice underwent 6 h of restraint stress per day for a total of 21 days. 24 h following the last restraint stress session the mice were sacrificed and the brains extracted for Golgi staining and analysis. Chronic restraint stress during adolescence promoted opposing effects on dendritic spine density in the prelimbic cortex, with a stress-induced increase in Nrg1 HET mice and a decrease in WT mice. Stress-induced reductions in dendritic complexity in the prelimbic cortex were more pronounced in Nrg1 HET mice relative to WT mice. Stress promoted greater dendritic spine atrophy in Nrg1 HET than WT mice in the CA1 region of the hippocampus. Nrg1 HET mice appeared to confer resilience to stress-induced dendritic spine atrophy in the infralimbic cortex, as stressed WT mice displayed reduced dendritic spine density compared to controls, whereas no significant changes were observed between stressed and non-stressed Nrg1 HET mice. Interestingly, Nrg1 hypomorphism did not influence the effects of stress on the basolateral amygdala, as stress increased dendritic spine density equally in both WT and Nrg1 HET mice. We also show for the first time that partial genetic deletion of Nrg1 alone promoted dendritic spine density reductions in the CA3 region of the hippocampus. The present results confirm that Nrg1 deficiency during adolescence modulates the effects of stress on dendritic morphology.

Disclosures: D.J. Clarke: None. **T. Chohan:** None. **M.S. Kassem:** None. **S.Y. Fok,:** None. **M.R. Bennett:** None. **J.C. Arnold:** None.

Poster

770. Psychosis: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 770.27/E12

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: Mutations in the BLOC-1 subunits dysbindin, muted, and pallidin regulate levels of excitatory and inhibitory markers in the hippocampus

Authors: M. ARNOLD[1], *J. L. LARIMORE[2], V. FAUNDEZ[3];
[1]Agnes Scott Col., Atlanta, GA; [2]Biol. Dept., Agnes Scott Col., Decatur, GA; [3]Emory Univ., Atlanta, GA

Abstract: Dysbindin protein levels are reduced in post-mortem brains of patients diagnosed with Schizophrenia (SZ). Dysbindin and its interacting proteins, including BLOC-1 complex members, may also be involved in disease pathogenesis. Current theories in SZ research hypothesize symptoms may be due in part to an imbalance in the excitatory and inhibitory (E/I) signals in cortex and hippocampus. To determine if dysbindin and BLOC-1 complex members may regulate E/I balance, we examined mRNA and protein levels of E/I markers in the hippocampus of mice null for BLOC-1 alleles. We propose that different subunits of the BLOC-1 complex have different phenotypic presentation therefore contributing to the wide spectrum and complexity of neurodevelopment disorders.

Disclosures: M. Arnold: None. **J.L. Larimore:** None. **V. Faundez:** None.

Poster

770. Psychosis: Animal Models

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Support: 14JC1403700

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2013YQ030923

Shanghai Eastern Scholar Tracking Program

Title: Knockdown BCL9 by using *in utero* electroporation results in neural developmental and electrophysiological deficits via Wnt signaling pathway

Authors: *W. LI;
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Abstract: B-cell CLL/lymphoma 9 (BCL9) was identified in a B-cell acute lymphoblastic leukemia cell line, and associated with tumor progression via β-catenin and Wnt signaling pathway. The association studies suggested that BCL9 was also related to schizophrenia and bipolar disorder. However, the function of BCL9 in the brain is poorly understood. Here, we found that BCL9 was highly expressed in mouse brain during development and knockdown BCL9 in the neural system could significantly altered the Wnt signaling pathway. Interestingly, knockdown of BCL9 by using *in utero* electroporation could severely disturb the migration of cortical neurons, and the affected migrating neurons displayed aberrant action potentials. Our findings indicated that elimination of BCL9 function in the brain might contribute to the pathogenesis of developmental neuropsychiatric disorders.

Disclosures: W. Li: None.

Poster

770. Psychosis: Animal Models

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Topic: F.02. Animal Cognition and Behavior

Support: The Italian Institute of Technology (IIT)

the Marie Curie FP7-Reintegration-Grant N°268247

the Italian Ministry of Health Grants (GR3)

Title: Development of schizophrenia-relevant cognitive abnormalities during adolescence: a translational study in mice

Authors: *M. CIAMPOLI, F. PAPALEO;
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Abstract: A microdeletion of the chromosome 22 band q11.2 results in the so called 22q11.2 deletion syndrome (22q11DS). By late adolescence/early adulthood up to one-third of patients with 22q11DS develop schizophrenia, making 22q11DS the most commonly known genetic syndrome associated with this psychiatric disorder. In an effort to set the ground towards the development of early detection and early intervention strategies relevant to schizophrenia, we developed a set of preclinical tasks enabling to assess preadolescent-adolescent development of behavioral phenotypes relevant to schizophrenia. In particular, we are applying this newly-developed battery of tasks to LgDel mutant mice that carry the same 1.5 Mb deletion of the human 22q11DS. This mouse model is a unique tool to validate and elucidate early developmental abnormalities relevant to schizophrenia. Despite this, no studies had so far checked the impact of the 22q11 microdeletion in behavioral phenotypes from birth to adolescence in mice. We first set the best experimental conditions to characterize Startle and Pre-Pulse Inhibition (PPI) abilities from pre-pubertal to adolescent. Using these settings we unraveled altered startle responses in the LgDel mice at pre-pubertal (PND 14) ages. Moreover we found that sensorimotor gating deficits in LgDel mice started to appear during adolescence (PND 35). Next, we implemented a modified version of the 5-Choice Serial Reaction Time Task (5CSRTT) in order to be able to measure attentional control in adolescent mice. Adolescent wild type mice were able to acquire and perform this new paradigm, advancing across the different stages and environmental manipulations in less than fifteen days (PND 24-36). We are now testing LgDel mice. Overall, our experiments are starting to elucidate new ways to test also in mice schizophrenia-relevant phenotypes. This will be important in the context of the development of early therapeutic intervention in schizophrenia.

Disclosures: **M. Ciampoli:** None. **F. Papaleo:** None.

Poster

770. Psychosis: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 770.30/E15

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant KL2 TR000081

Hope for Depression Research Foundation

Title: Behavioral pattern separation in a transdiagnostic anxiety population

Authors: *K. C. KLEMENHAGEN[1], R. HEN[2], H. B. SIMPSON[3,4], A. J. FYER[3];
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Abstract: Animal model studies have demonstrated a role for adult neurogenesis within the dentate gyrus of the hippocampus in anxiety-like behavior and in responses to stress. One paradigm tested in these animal models is behavioral pattern separation. Electrophysiologists first described pattern separation in the hippocampus, where neurons within the circuitry of the hippocampus are thought to discriminate between similar inputs. At a higher level of organization, behavioral pattern separation refers to behavioral discrimination between similar stimuli. Behavioral pattern separation is negatively affected by manipulations causing loss of adult neurogenesis in animal models, and by mild cognitive impairment (C. Stark) and binge drinking and stress (S. Becker) in humans. Here, we apply the Behavioral Pattern Separation - Objects / Mnemonic Similarity test of Stark and the Concentration Matching Task (spatial pattern separation) of Becker to a transdiagnostic sample of anxiety patients and controls. We hypothesize that a subset of anxious patients cutting across diagnosis categories will have deficits in behavioral pattern separation, which may contribute to their mood disorder. Furthermore, behavioral pattern separation performance may positively correlate with self-report measures of mood, and with report of physical activity, a dramatic modulator of neurogenesis levels in animal models, in both patients and controls. The ability to identify a group of patients with putative decreases in adult neurogenesis via translational behavioral paradigms will help to develop individual-specific treatments for mood disorders, as well as contribute to stratification of patients for more effective studies of novel treatments targeting hippocampal adult neurogenesis.

Disclosures: K.C. Klemenhagen: None. **R. Hen:** None. **H.B. Simpson:** None. **A.J. Fyer:** None.

Poster

771. Psychosis: Biochemistry

Location: Hall A

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Program#/Poster#: 771.01/E16

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: ISF Grant 2016809

Title: Abnormalities in the assembly process of mitochondrial complex I in schizophrenia: a possible cause for mitochondrial dysfunction

Authors: *O. BERGMAN[1], R. KARRY[2], D. BEN-SHACHAR[3];
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[3]Lab. of Psychobiology, Dept. of Psychiatry, Rambam Hlth. Care Campus, the Ruth and Bruce Rappaport Fac. of Medicine, Technion-Israel Inst. of Technology., Haifa, Israel

Abstract: Abnormalities in mitochondrial oxidative phosphorylation system are observed in several mental disorders including schizophrenia, specifically in complex I (CoI). We have previously reported altered mRNA and protein levels of the labile subunits of CoI: NDUFV1, NDUFV2 and NDUFS1, in brain postmortem specimens and peripheral cells of schizophrenia patients. Notably, patients diagnosed with CoI deficiency portray a variety of schizophrenia-like symptoms. We therefore hypothesize that holo-CoI assembly may contribute to mitochondrial dysfunction in schizophrenia. Mitochondria were isolated from Epstein-Barr virus (EBV) transformed lymphocytes of schizophrenia patients and healthy subjects. Clear-native PAGE CoI in-gel activity assays also showed a significant reduction in schizophrenia cell lines (69.6±11.8 vs. 113.6±10.9 OD/mg protein/hr, P=0.008). While blue-native PAGE showed no difference in CoI holoenzyme protein levels, its sub/super-complexes, its synthesis rate, determined by the incorporation of 35S-methionine labeled mitochondrial subunits into holo-CoI, was significantly lower in patient cell lines (2.3±0.6 vs. 0.65±0.15, normalized OD, P=0.01). The synthesis rate of the mitochondrial subunits did not differ between the two cohorts. However, the import of in-vitro translated 35[S]-methionine labeled NDUFV2 labile subunit of patients was impaired. Both patient-derived mitochondria and protein synergistically contributed to this decreased import. Concomitantly, mitochondria/cytosol ratio of NDUFV1 and NDUFV2 protein/pre-protein was reduced in schizophrenic cells. Interestingly, protein levels, detected by immunoblotting, of 8 different subunits of CoI were similar in healthy and patients samples. However, only the labile subunits showed a significantly higher coefficient of variance in control compared to patient samples, suggesting a slower exchange of this preexisting CoI subunits for newly imported ones, which may hinder this repair process. These abnormalities were associated with reduced CoI-driven respiration as well as with a pathological interaction of CoI with dopamine, a major substance in schizophrenia, in patients as compared to healthy subjects. Taken together, the data suggest that impairment in labile subunits incorporation into the holo-CoI in schizophrenia, which occur at the final stage of assembly, contributes to its abnormal activity and thereby to mitochondrial multifaceted dysfunction reported in schizophrenia.

Disclosures: O. Bergman: None. **R. Karry:** None. **D. Ben-Shachar:** None.

Poster

771. Psychosis: Biochemistry

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Program#/Poster#: 771.02/E17

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: W81XWH-- 11-- 2-- 0166

Title: MicroRNA level reductions in Mediodorsal thalamus with 5HTTLPR-SS genotype

Authors: *K. A. YOUNG, E. S. CARTER, D. L. PAPPALARDO-CARTER;
Psychiatry & Behavioral Sci., Texas A&M HSC / Central Texas VA, Temple, TX

Abstract: The mediodorsal thalamus (MD) provides powerful glutamateric input to the frontal cortex and is an important node in limbic circuitry. We have previously observed neuronal loss in this nucleus in older cases with schizophrenia (SKZ), elevated numbers of neurons in a younger cohort of major depression (MDD) cases, and a strong influence of the serotonin transporter 5HTTLPR genetic variant on thalamic neuron populations. Most recently, we observed alterations in microRNAs (miRs) in both MDD and SKZ and global deficits in miR levels in suicide cases in the MD. In the present study, we examined the influence of 5HTTLPR on miR levels in the MDD. MiR levels and 5HTTLPR genotype with rs23456 following the "triallelic" convention were assessed in RNA/DNA extracted from frozen MD specimens of the Stanley Foundation Research Consortium (12 MDD, 12 SKZ and 14 controls) using PCR and Exiqon Human miRnome V1.M RT-PCR panels, resulting in an N = 577 MD-expressed miRs. A common pattern was that 5HTTLPR SS alleles were associated with reduced miR levels compared to SL genotype across many miR species, as evidenced by a significant reduction in total miR load ($p<0.027$), controlling for diagnosis, age, gender and PMI. The most reliably affected SL>SS miRs (abundant miRs with p's <0.02) included miRs-7d*, 1979, 320a, 432, 532-5p, 664 and 92b. Interestingly Mir-432, which targets ELK1 (a transcription factor binding to 5HTTLPR), has previously been found to be decreased in SKZ blood. The 7 SS-reduced miRs targeted PTPRD, CNIH, FAM19b, and TOB1 mRNAs as a group. Several of these genes have been previously associated with either SKZ (CNIH, TOB1 and PTPRD) or MDD (TOB1). MiR-377 had the most reliable evidence for elevated levels compared to SL/LL. Several miRs expressed at relatively low levels displayed significantly altered but skewed distributions suggestive of selective miR editing in SS or LL genotypes, with loss of probe annealing potentially due to edited miR sequences. There was no relationship between 5HTTLPR genotype and MD mRNA levels for DGCR8, Drosha or Dicer transcripts. The present data support a pathophysiological phenotype consisting primarily of reduced miR levels in the MD nucleus of the thalamus associated with the 5HTTLPR-SS genotype.

Disclosures: K.A. Young: None. **E.S. Carter:** None. **D.L. Pappalardo-Carter:** None.

Poster

771. Psychosis: Biochemistry

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Program#/Poster#: 771.03/E18

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: The Lundbeck Foundation Initiative for Integrative Psychiatric Research Grant

Title: Neuroproteomic changes caused by decreased expression of the schizophrenia and bipolar disorder associated BRD1 gene in mice

Authors: *J. H. CHRISTENSEN[1,2,3], V. PATERNOSTER[1,2,3], M. SVANBORG[1,2,3], A. V. EDHAGER[4], A. P. RAJKUMAR[1,2,3], P. QVIST[1,2,3], T. FRYLAND[1,2,3], E. A. EICKHARDT[1,2,3], J. PALMFELDT[4], A. D. BØRGLUM[1,2,3];
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Abstract: Genetic evidence has repeatedly implicated the *BRD1* gene in schizophrenia and bipolar disorder. The BRD1 protein is involved in histone modification and regulates the expression of genes located adjacent to its genomic binding sites. *Brd1*$^{+/-}$ mice show behavioural phenotypes congruent to schizophrenia and depression symptoms, accompanied by disturbances in neurochemistry, imbalanced excitatory-inhibitory neurotransmission and changes in neuronal morphology. In order to dissect the molecular changes underlying the phenotypes in female *Brd1*$^{+/-}$ mice, which show reversible depression-like behaviours as well as cognitive deficits, we performed quantitative neuroproteomic analyses of protein extracts from frontal cortex, hippocampus and striatum using isobaric tagging of peptides combined with mass spectrometry using high-energy collision cells for fragmentation. In total, we detected more than 1500 proteins in each sample. We found varying numbers of differentially abundant proteins (DAPs) in the samples with as few as around 20 in whole-cell extracts from hippocampus and as high as 200-300 in extracts from frontal cortex. Ingenuity Pathway Analysis of the DAPs indicated among others that key signalling pathways for normal brain function (e.g. the dopamine, GABA and glutamate receptor signalling) are affected in female *Brd1*$^{+/-}$ mice. A total of 17 DAPs remained significant upon FDR control, all but one identified in frontal cortex samples. Strikingly, two of the proteins (LRP1 and TMX2) are encoded by genes that in humans are located in loci showing genome wide significant association with schizophrenia. Neuronal LRP1 seems to play a role in NMDA receptor-dependent intracellular signalling whereas the function of TMX2 remains

elusive. Of further notice, we found increased amounts of ARP2, ARP3, and their activator N-WASP in the cortex of female *Brd1*$^{+/-}$ mice. Loss of ARP2/3 function in excitatory neurons of the frontal cortex leads to a reduction in the number of normal axonal-spine synapses, enhanced pyramidal neuron excitation as well as frontal cortex–VTA/SNc circuit activation thereby elevating striatal dopamine (stDA) and inducing locomotion. We speculate whether reverted levels of these proteins could relate to the decreased stDA and normal (amphetamine non-inducible) locomotion seen in female *Brd1*$^{+/-}$ mice. In conclusion, we have mapped a number of neuroproteomic changes that collectively could explain the phenotypes of female *Brd1*$^{+/-}$ mice and pave the way for further dissection of its underlying causes.

Disclosures: J.H. Christensen: None. **V. Paternoster:** None. **M. Svanborg:** None. **A.V. Edhager:** None. **A.P. Rajkumar:** None. **P. Qvist:** None. **T. Fryland:** None. **E.A. Eickhardt:** None. **J. Palmfeldt:** None. **A.D. Børglum:** None.

Poster

771. Psychosis: Biochemistry

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Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: The Lundbeck Foundation Initiative For Integrative Psychiatric Research

The Augustinus Foundation

The Riisfort Foundation

Title: Glutamatergic dysregulation may cause neurotoxic effects and loss off parvalbumin fast-spiking interneurons in developing Brd1+/- mice

Authors: *T. FRYLAND[1,2,3], P. QVIST[1,2,3], A. RAJKUMAR[1,2,3], M. NYEGAARD[1,2,3], O. MORS[4,3], T. J. CORYDON[1,2,3], A. D. BØRGLUM[1,2,3], J. H. CHRISTENSEN[1,2,3];
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Abstract: The bromodomain-containing 1 gene (BRD1) gene has been implicated with brain development and susceptibility to psychiatric disorders. BRD1 interacts in a histone acetyltransferase complex with K(lysine) acetyltransferase 7 KAT7 (also known as HBO1 or MYST2) and the BRD1 chromatin and protein interaction network is enriched for schizophrenia

risk genes. Further investigations of Brd1+/- KO mice identified global cerebral hypo-acetylation of histone H3K14 combined with schizophrenia-associated behaviors, cognitive deficits and altered cortical inhibitory neurotransmission. Whole transcriptome profiling (RNA-seq) on striatal and cortical tissue from Brd1+/- and WT mice have identified expression of genes encoding synaptic proteins implicated in glutamatergic signaling, as well as a lowered expression of the marker for fast-spiking interneurons, parvalbumin (Pvalb) in Brd1+/- compared to WT mice. We hypothesized that excitocytoxicity cause the loss of fast-spiking, pvalb+ interneurons and that this neurotoxic effect can be rescued by restoring the normal histone acetylation level. To investigate this, we examined the maturation of inhibitory networks in developing primary cortical cultures derived from Brd1+/- and WT P0 mice. Cells were cultured for 12, 18, and 24 DIV before they were fixed and IF stained using Nf200, Psd-95, Pvalb and Gad67 antibodies. We found that cultures from Brd1+/- mice mature later than WT and further degenerate faster with fractions of mature neurons (incl. GABAergic neurons) being lower at both 12 and 24 DIV but not 18 DIV. In line with our data from mouse brains and supporting our hypothesis, we found an accelerated decrease of Pvalb+ neurons and a significant increase in neurite Psd-95 puncta density at 18 and 24 DIV in Brd1+/- cultures compared to WT. In order to find a suitable drug for reversing the effect of reduced Brd1 expression and thus hypo-acetylation, we correlated our RNA-seq data with brain expression data from mice treated with HDACi 4b (Jia et al. 2014) and identified a negative correlation of differentially expressed genes involved in glutamatergic signaling. We are currently testing the effect of both HDACi 4b and valproic acid using IF staining, RNA-seq, and ChIPseq in order to monitor a potential rescue on the level of phenotype, gene expression and histone acetylation in primary neurons derived from Brd1+/- and WT mice. The results from this analysis will be presented at the conference.

Disclosures: **T. Fryland:** None. **P. Qvist:** None. **A. Rajkumar:** None. **M. Nyegaard:** None. **O. Mors:** None. **T.J. Corydon:** None. **A.D. Børglum:** None. **J.H. Christensen:** None.

Poster

771. Psychosis: Biochemistry

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Program#/Poster#: 771.05/E20

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: The Lundbeck Foundation initiative for Integrative Psychiatric Research (iPSYCH)

The Augustinus Foundation

The Riisfort Foundation

Title: The implication of the schizophrenia-associated BRD1 gene in brain morphology

Authors: *P. L. QVIST[1], S. F. ESKILDSEN[2], S. RINGGAARD[3], H. STODKILDE-JORGENSEN[3], O. MORS[4], A. D. BORGLUM[5], J. H. CHRISTENSEN[5];
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Abstract: Schizophrenia is a common and devastating disorder but its etiology remains largely unknown. Whereas pharmacological and genetic studies have collectively pointed to underlying deficits relating to neuro-differentiation, -development and -plasticity, no clear structural basis for the disorder has been established. The bromodomain-containing 1 (BRD1) gene has been implicated with both brain development and susceptibility to schizophrenia and male mice with decreased Brd1 expression (Brd1+/- mice) display schizophrenia-associated behaviors and altered striatal dopamine transmission. In the present study we attempt to determine the correlation between reduced Brd1 expression and cerebral pathology in male Brd1+/- mice using magnetic resonance imaging (MRI). MR images of eight 15 weeks old freshly sacrificed adult male mice (4 Brd1+/- and 4 wild type (WT)) were acquired with a 9.4T Agilent small-bore scanner (Agilent, Santa Clara, CA, USA) using a 20-mm surface coil (RAPID Biomedical Rimpar, Germany) for signal reception. The images were acquired using a 3D fast gradient echo sequence with repetition time (TR) = 13.7 ms, echo time (TE) = 6.9 ms, flip angle = 20°, matrix size = 400 × 400 × 400, field-of-view = 4.0 × 4.0 × 2.0 cm, spatial resolution = 100 × 100 × 50 μm (highest resolution in coronal direction), number of averages = 4, and acquisition time = 2:26 hours. An average model fitting the C57Bl/6j mouse brain atlas was created from images from the eight pilot scans and 52 labels from the atlas were then mapped to the individual images. In this study, we observed no overall changes in cerebral volume between Brd1+/- and WT mice and we did not find any differences in ventricle volumes as has repeatedly been reported in patients with schizophrenia. However, despite the low number of animals included, we observed nominally significant volumetric differences in several brain regions. Particularly the striatum appeared to be reduced in Brd1+/- mice compared to WT mice, thus potentially establishing a link between the molecular, biochemical and behavioral findings in Brd1+/- mice and a neuropathological phenotype. Although more mice need to be included in the study and our findings need to be validated by stereological measures in fixed brains, our preliminary data suggest Brd1 is implicated in brain architecture in mice.

Disclosures: P.L. Qvist: None. **S.F. Eskildsen:** None. **S. Ringgaard:** None. **H. Stodkilde-Jorgensen:** None. **O. Mors:** None. **A.D. Borglum:** None. **J.H. Christensen:** None.

Poster

771. Psychosis: Biochemistry

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Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: MRC IGMM PhD Studentship

Title: Defective axonal mitochondrial trafficking in a DISC1 translocation mouse model

Authors: *L. MURPHY[1], E. L. V. MALAVASI[1], H. S. TORRANCE[1], M. DIDIER[2], D. J. PORTEOUS[1], J. K. MILLAR[1];
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Abstract: Disrupted In Schizophrenia 1 (DISC1) was first identified as a candidate gene for major mental illness due to its disruption by a balanced t(1;11) translocation that co-segregates with psychiatric illness in a large Scottish family. DISC1 regulates the trafficking of mitochondria in axons and this potentially implicates mitochondrial homeostasis in psychiatric illness. We have access to a novel mouse model of the t(1:11) translocation developed by Sanofi. Compared to wild type mice, heterozygous t(1;11) mice exhibit reduced DISC1 mRNA and protein expression, consistent with the reduced DISC1 expression levels in lymphoblastoid cell lines derived from translocation carriers in the Scottish family. To test for potential effects of the t(1:11) translocation on axonal mitochondrial trafficking, hippocampal neurons isolated from homozygous and wild type mouse embryos were used for time-lapse imaging of mitochondrial motility. Measurements were collected from fifty axon segments over three independent cultures of neurons from each genotype. Several parameters were analysed, including percentage motility, direction of movement, and displacement. No change in the number of moving mitochondria, or their direction of movement was detected. However, net displacement of retrograde, but not anterograde, moving mitochondria was significantly lower in homozygous versus wild type neurons, lending additional support to our hypothesis that mitochondrial trafficking defects increase susceptibility to psychiatric illness.

Disclosures: L. Murphy: None. **E.L.V. Malavasi:** None. **H.S. Torrance:** None. **M. Didier:** None. **D.J. Porteous:** None. **J.K. Millar:** None.

Poster

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Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: MRC project grant G0902166

Wellcome Trust-University of Edinburgh Institutional Strategic Support Fund

Title: Regulation of trafficking of a surface protein by DISC1: a live cell imaging approach

Authors: *K. MILLAR[1], E. L. V. MALAVASI[1], M. DIDIER[2], Z. TARNAUSKAITE[3], D. J. PORTEOUS[1];
[1]Univ. of Edinburgh, Edinburgh, United Kingdom; [2]Sanofi, Paris, France; [3]Human Genet. Unit, Inst. of Genet. and Mol. Med. at the Univ. of Edinburgh, Edinburgh, United Kingdom

Abstract: The multifunctional scaffold protein Disrupted-In-Schizophrenia 1 (DISC1) is a risk factor for psychiatric disorders including major depression, bipolar disorder and schizophrenia. DISC1 is involved in many biological processes of central importance for neuronal development and function, including organelle trafficking. In axons, DISC1 regulates mitochondrial movement, a function that is likely mediated by its association with trafficking-protein-Kinesin-binding-1 (TRAK1), a protein that links mitochondria to kinesin and dynein for microtubule-based trafficking. DISC1 is also known to regulate the microtubule-based trafficking of synaptic vesicles and mRNA granules along neurites. If deregulated, all these processes have the potential to affect neuronal function, suggesting that the integrity of the trafficking function of DISC1 may be important for the maintenance of normal neuronal activity. Here, we hypothesised that DISC1 may also be involved in the regulation of the trafficking of surface proteins in neurons. To test this, we expressed surface protein X labelled with the photoconvertible fluorescent protein Dendra2 in hippocampal neurons and directly visualised the motility of X-Dendra2 in live dendrites. Bulk movement of X-Dendra2 molecules along dendrites was recorded by live confocal time lapse imaging after photoconversion of a small region within the dendrite, and fluorescence intensity data were analysed using a bespoke algorithm. We observed that X-Dendra2 molecules travel bidirectionally within dendrites, spreading proximally and distally from the photoconversion region. Overexpression of wild-type human DISC1 significantly reduced X-Dendra2 movement in the proximal direction, but had little or no effect on movement in the distal direction. By contrast, expression of the common single nucleotide variant DISC1-607F, which is associated with intermediate phenotypes for psychiatric illness, promoted the movement of X-Dendra2 towards the distal portion of dendrites, without affecting spreading in the proximal direction. To further test for the involvement of DISC1 in X-Dendra2 trafficking, we carried out the same measurements in hippocampal neurons isolated from a novel Disc1 mouse model in which expression of endogenous full-length Disc1 is lost. We observed that in null neurons, dendritic X-Dendra2 movement is reduced specifically in the proximal direction. Taken together, these results suggest for the first time that DISC1 may be involved in the

regulation of trafficking of surface-expressed proteins in neurons, with a possible modifying effect of a candidate disease-related DISC1 variant.

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Poster

771. Psychosis: Biochemistry

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Program#/Poster#: 771.08/E23

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: CREST

Title: Neurogranin deficiency causes neuronal immaturity in the dentate gyrus and frontal cortex of adult mice

Authors: *H. HAGIHARA[1,2], S. HATTORI[1,2], Y. TAKAMIYA[1,2], F. L. HUANG[3], K.-P. HUANG[3], T. MIYAKAWA[1,2,4];
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Abstract: Previous genome-wide association studies have suggested a link between schizophrenia and neurogranin (Nrgn), a neuron-specific protein abundantly expressed in brain regions implicated in memory and cognitive function, such as the hippocampus and cortex (Stefansson et al, 2009; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Nrgn knockout (KO) mice exhibit schizophrenia-relevant behavioral phenotypes, such as increased locomotor activity, abnormal anxiety-like behavior, impaired social behavior, and working memory deficits (Miyakawa et al, 2003; Hattori et al, this meeting). However, the molecular alterations underlying these behavioral abnormalities are still unclear. We previously reported that in the patients with psychiatric disorders, such as schizophrenia and bipolar disorder, and in some animal models of these disorders, certain cell types in the hippocampal dentate gyrus (DG) and frontal cortex are in a pseudo-immature status (Yamasaki et al, 2008; Walton et al, 2012; Ohira et al, 2013; Takao et al, 2013; Hagihara et al, 2014). Based on the findings, we proposed that the pseudo-immaturity of the brain cells might be an endophenotype of these psychiatric disorders (Hagihara et al, 2013). Here, we investigated whether Nrgn KO mice exhibit this phenotype in their brain. In the DG, mRNA expressions of immature and

mature granule cell (GC) markers were not changed in almost all young Nrgn KO mice (20 weeks old) showed increased expression of immature GC markers and decreased expression of mature GC markers in the DG, suggesting a pseudo-immature phenotype. This suggests that both undetermined (e.g., stress and aging) and genetic factors might act together to reverse matured GCs to a pseudo-immature status. Interestingly, immunohistochemical analyses revealed patch-like expression for calbindin, a marker of mature GCs, in the DG of older mice. Patch-like expressions of several genes including calbindin have been shown in the cortex of patients with autism (Stoner et al, 2014). In our mutant mice, the medial frontal cortex had decreased number of cells expressing parvalbumin, which could be used as a marker of mature fast-spiking interneurons, without a gross decrease in cell density, suggesting another pseudo-immature phenotype. Decreased parvalbumin level is also observed in the cortex of patients with schizophrenia. Together, these findings suggest that Nrgn deficiency causes pseudo-immaturity in certain types of neurons in the DG and frontal cortex. Our results are consistent with the idea that neuronal immaturity in the brain is an endophenotype of schizophrenia.

Disclosures: H. Hagihara: None. **S. Hattori:** None. **Y. Takamiya:** None. **F.L. Huang:** None. **K. Huang:** None. **T. Miyakawa:** None.

Poster

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Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: the Core Research for Evolutional Science and Technology of Japan Science and Technology Agency (JST-CREST)

Ministry of Education, Culture, Sports, Science and Technology Grants-in-Aid for Scientific Research (KAKENHI)

Title: Neurogranin-deficient mice reveal schizophrenia-related behaviors and immaturity of the dentate gyrus

Authors: *S. HATTORI[1], H. HAGIHARA[1], H. SHOJI[1], Y. TAKAMIYA[1], F. L. HUANG[2], K.-P. HUANG[2], T. MIYAKAWA[1,3];
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Abstract: Through a genome-wide association studies for schizophrenia, single nucleotide polymorphisms of the Neurogranin (NRGN) gene have been confirmed to be associated with the disorder. In addition, neurogranin immunoreactivity has been shown to be dramatically decreased in the prefrontal cortex of patients with schizophrenia. These findings suggest that NRGN is one of the most promising risk genes for schizophrenia. Neurogranin is a neuronal postsynaptic protein C kinase substrate that is abundantly expressed in brain regions important for cognitive function, including the hippocampus and cortex. Previous studies indicated that neurogranin is involved in synaptic plasticity and long-term potentiation and that knockout (KO) of Nrgn leads to aberrant behavioral phenotypes involving deficits in cognitive functions and abnormal emotional behaviors in mice. To further investigate the functional roles of neurogranin in the central nervous system, we subjected Nrgn KO mice to a comprehensive battery of behavioral tests. Consistent with the results of previous studies, increased locomotor activity, abnormal anxiety-like behavior, impaired social behavior, and deficits in working memory were observed in Nrgn KO mice. The mutant mice also exhibited abnormal depression-like behaviors and impaired sensorimotor gating. In addition, the dentate gyrus in the adult mutant mice exhibited an immature phenotype, which has been proposed as a novel endophenotype of psychiatric disorders, including schizophrenia. These observations collectively indicate that Nrgn KO mice may represent a novel animal model of schizophrenia.

Disclosures: S. Hattori: None. **H. Hagihara:** None. **H. Shoji:** None. **Y. Takamiya:** None. **F.L. Huang:** None. **K. Huang:** None. **T. Miyakawa:** None.

Poster

771. Psychosis: Biochemistry

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 771.10/E25

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: Pentosidine accumulation in the pathophysiology of schizophrenia

Authors: *M. ARAI[1], Y. HORIUCHI[1], A. KOBORI[1], M. MIYASHITA[1], K. TORIUMI[1], S. HATAKEYAMA[1], M. ITOKAWA[1], H. HASHIMOTO[2];
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Abstract: Genetic and environmental factors are thought to be involved in the pathogenesis of schizophrenia. Despite extensive efforts to clarify the underlying disease mechanisms, the main cause and pathophysiology of schizophrenia remains unclear. The lifetime prevalence is

approximately one percent, with onset of disease frequently occurring in early adulthood. We previously reported that a certain subtype of schizophrenic patients exhibit idiopathic carbonyl stress with high plasma pentosidine levels and serum vitamin B6 depletion, which is referred to as carbonyl stress, without underlying diabetes or chronic kidney disease that are the two major cause of elevation of advanced glycation end products (AGEs). Furthermore, we found the correlation between carbonyl stress and clinical features such as high ratio of inpatients, long duration of hospitalization, higher daily doses of anti-psychotics and lower educational status, suggesting that those patients might be treatment-registrant cases. We attempted to find associations between cognitive impairments and biochemical data. Schizophrenics were divided into four groups by their levels of pentosidine and vitamin B6, and we assessed the symptom severity by the Manchester Scale Japanese version (MS-J), the cognitive function by Wechsler Adult Intelligence Scale 3rd version (WAIS-III) and Wisconsin card sorting test (WCST). We found that symptoms in high-risk group with high pentosidine and low vitamin B6 had a tendency to severe incoherence of thought and lower performance for digit span compared to that of other groups. Our preliminary data suggest that carbonyl stress might be associated with impaired working memory in schizophrenia. The comprehensive information covering *in vitro* and *in vivo* studies is important for evidence-based personalized medicine and hopefully more effective treatment for schizophrenic patients.

Disclosures: **M. Arai:** None. **Y. Horiuchi:** None. **A. Kobori:** None. **M. Miyashita:** None. **K. Toriumi:** None. **S. Hatakeyama:** None. **M. Itokawa:** None. **H. Hashimoto:** None.

Poster

771. Psychosis: Biochemistry

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 771.11/E26

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: Abnormal glutathione pathway in postmortem dorsolateral prefrontal cortex from people with schizophrenia

Authors: *Y. ZHANG, V. S. CATTS, C. S. WEICKERT;
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Abstract: Oxidative stress is associated with increased production of reactive oxygen species (ROS) and decreased antioxidant defences. Increased oxidative stress can cause tissue injury and cellular damage in the central nervous system. The glutathione (GSH) pathway is the most important antioxidant system to protect against oxidative stress in human brain. GSH is

biologically synthesized by the rate-limiting enzyme glutamyl-cysteine ligase (GCL). GSH exists in a reduced form (GSHR) which is oxidized to GSSG when ROS are detoxified by GSH peroxidase (GPx). In this study, we examined the GSH antioxidant system in post-mortem brain from patients with schizophrenia. The quantities of glutamyl-cysteine ligase subunit C (GCLC), GSHR and total GSH in the pathway were measured. It is hypothesized that an abnormal GSH pathway is associated with schizophrenia. Dorsolateral prefrontal cortex from 37 schizophrenia cases and 37 matched controls were studied. Western blotting was used to examine the GCLC protein levels. The levels of GSHR and total GSH were determined by spectrophotometry. The difference in the GCLC and GSH levels between schizophrenia and controls were analysed by independent t-test analysis. We found that there is no significant difference [t(72)-1.077, p=0.285] in the levels of GCLC/β-actin between people with schizophrenia (1.67+0.58) and control subjects (1.55+0.55). However, we found that levels of GSHR/internal control in schizophrenia (1.05+0.25) were significantly less than in control subjects (1.23+0.25) [t(66)3.048, p=0.003]. Moreover, we found that levels of total GSH/internal controls in schizophrenia (1.01+0.25) were significantly less than in controls (1.16+0.21) [t(66)2.615, p=0.011]. In our study, there was no difference of the GCLC level between schizophrenia and controls; but less GSHR and less total GSH in people with schizophrenia than in controls. A decrease in GSHR and total GSH indicate impaired antioxidant defences in the prefrontal cortex of people with schizophrenia. In future studies, GPx protein will be measured to determine if it is consistent with our measures of GSH. Furthermore, we will seek to determine how oxidative stress relates to other neuropathological changes (i.e. increased inflammation) in schizophrenia.

Disclosures: Y. Zhang: None. **V.S. Catts:** None. **C.S. Weickert:** None.

Poster

771. Psychosis: Biochemistry

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 771.12/E27

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: iBrain/HHUD

NARSAD /BBR Independent Investigator Award (#20350)

EU-FP7 MC-ITN IN-SENS (#607616).

Title: Autofluorescence as a quantitative measurement of schizophrenia patient-derived lymphoblast responses to stress

Authors: *X. INDURKHYA[1], A. RAMOS[2], N. ELKINS[2], T. TSUJIMURA[2], K. ISHIZUKA[2], A. SAWA[2], C. KORTH[1];
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Abstract: Background The accumulation of autofluorescence (AF) within a cell is understood to be part of the normal aging process. This AF, termed lipofuscin, is the exclusive criteria for the definition of ceroid, which is any non-lipofuscin AF. After the discovery by the Sawa lab of elevated AF in cell lines derived from schizophrenic patients, we investigated this AF as schizophrenia-related ceroid. We tested the response of this ceroid to stress and investigated whether riboflavin was the source of the AF. **Methods** Lymphoblast lines derived from the immortalized lymphocytes of schizophrenia patients (n=8) and controls (n=7) were used for this study. FAD concentrations were measured in all cell lines. Cells were synchronized with serum starvation, treated with extra riboflavin (30 μM) and treated with oxidative stressors rotenone (10 μM) and hydrogen peroxide (100 μM). Results were analyzed via the largest AF peak identified in the cells at ex450/em530. AF was analyzed with photospectroscopy conducted in a microplate reader on live cells; alternatively, autofluorescent speckles were counted on images of fixed cells obtained via fluorescence microscopy with standard GFP filters (ex470/40, em525/50). **Results** There was no significant difference in the FAD concentrations of schizophrenia cell lines as compared to controls. The addition of riboflavin appeared to have no effect on the AF, except to cause an indiscriminate increase in intensity. However, serum starvation synchronization and rotenone appeared to affect the schizophrenia lines differently from the controls. **Discussion** Our results suggest that while riboflavin may be involved in the disease and even a component of the AF, it is not the principle source. Based on our data, there may be two schizophrenia subtypes: one with diminished FAD and one with elevated FAD. The schizophrenia patient-derived cells demonstrated a hypersensitivity to the oxidation-induced AF. They simultaneously showed insensitivity to the starvation-induced AF observed in control lines. Thus, we can narrow down the molecular source of the AF to distinct cellular circuitry.

Disclosures: X. Indurkhya: None. **A. Ramos:** None. **N. Elkins:** None. **T. Tsujimura:** None. **K. Ishizuka:** None. **A. Sawa:** None. **C. Korth:** None.

Poster

771. Psychosis: Biochemistry

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Program#/Poster#: 771.13/E28

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: NIMH Grant R01 MH097803

NINDS Grant R01 NS065052

SFAz Bisgrove Scholarships

Title: Influence of schizophrenia-associated gene Egr3 on sleep and wakefulness in mice

Authors: *A. M. MAPLE[1], R. K. ROWE[3,2,4], J. L. HARRISON[3,2,5], A. K. MCBRIDE[1], I. FERNANDEZ[6], J. LIFSHITZ[3,5,2,4], A. L. GALLITANO[1];
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Abstract: Sleep abnormalities are a common symptom in psychiatric disorders. Approximately 30-80% of patients with schizophrenia report disturbed sleep. The most common disturbances reported in patients are reduced sleep efficiency, decreased total sleep time, and increased sleep latency. However, the cause of sleep disturbances in schizophrenia is unknown. Both genetic and environmental factors influence schizophrenia risk. The immediate early gene (IEG) early growth response 3 (*Egr3*) has been associated with schizophrenia risk in human populations and decreased levels of EGR3 protein have been found in postmortem brain tissue from patients. *Egr3*-deficient mice display behaviors associated with schizophrenia pathophysiology. Interestingly, exposure to light induces high levels of *Egr3* expression in the suprachiasmatic nucleus (SCN), a brain area critical for circadian rhythms. The potential roles of *Egr3* in both schizophrenia and the response of SCN neurons to light led us to hypothesize that loss of *Egr3* may disrupt sleep-wakefulness regulation in mice. To test this hypothesis, male and female adult wild type (WT) and *Egr3 -/-* mice were monitored for one week in individual, non-invasive sleep monitoring cages. This system uses piezoelectric materials as highly-sensitive pressure detectors to determine a sleep profile for each animal. We found that male and female *Egr3 -/-* mice slept less compared with WT mice and that these differences were most profound during light/dark transitions. Female mice of both genotypes slept less than male mice, demonstrating an effect of gender on sleep. These data suggest that *Egr3* contributes to cumulative sleep and thus support our hypothesis. Notably, serotonin 2A receptor (5-HT_{2A}R) deficient mice also display a similar decrease in overall sleep compared to WT mice as that we found in *Egr3 -/-* mice. Prior findings from our laboratory suggest that *Egr3* may regulate cortical 5-HT_{2A}R expression. Similar sleep disruptions in *Egr3* and 5-HT_{2A}R deficient mice are additional support that thesegenes may interact functionally. Future studies determining additional biological mechanisms that contribute to sleep abnormalities may increase our understanding of pathophysiology of schizophrenia and other psychiatric disorders.

Disclosures: **A.M. Maple:** None. **R.K. Rowe:** None. **J.L. Harrison:** None. **A.K. McBride:** None. **I. Fernandez:** None. **J. Lifshitz:** None. **A.L. Gallitano:** None.

Poster

771. Psychosis: Biochemistry

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 771.14/E29

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: NIH R01MH085666 to Wen-Jun Gao

Title: Developmental decline of NR2B expression in PFC in the MAM model for schizophrenia: consequences and mechanism

Authors: *Y. GULCHINA, M. A. SNYDER, W.-J. GAO;
Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: The prefrontal cortex (PFC) encodes cognitive features that are integral for appropriate behavioral response to environmental demands. In particular, working memory function is an essential constituent process of prefrontal-dependent higher order cognitive functions. The NMDA receptor is a molecular substrate of learning and memory functions, with the NR2B subunit intimately linked to working memory. In schizophrenia (SCZ), working memory and other prefrontal-dependent cognitive functions are impaired prior to the emergence of psychosis, and patients' functional capabilities are directly dictated by these impairments. Thus, it seems likely that NMDA, particularly NR2B, dysfunction is a feature of early cognitive decline in this disorder. Given the unique profile of NR2B expression in the developing brain, we hypothesize that disrupted NR2B expression in an animal model for SCZ is the crux of early cognitive deficits in this disorder. We utilized the MAM model for SCZ to address this hypothesis. Our data support that downregulation of NR2B is a feature of juvenile (p21) and adolescent (p45) development in PFC in MAM-exposed animals via Western blot and whole-cell patch clamp recording. We observed that layer V pyramidal neurons from juvenile MAM-exposed rat medial PFC demonstrated a reduction in NMDA-mEPSC amplitude. Later, NMDA-mEPSC frequency was reduced in adolescent MAM-exposed animals. To confirm the synaptic nature of these deficits, we will proceed with evoked recordings of saline- and MAM-exposed medial PFC. Epigenetic mechanisms are well poised to contribute to this altered NR2B expression in MAM-exposed PFC. We have identified a selective increase in H3K27me3, a repressive histone modification, in juvenile MAM-exposed PFC. To further probe the role of epigenetic mechanisms in regulating NR2B expression, we will explore the role of repressor proteins, such as the REST complex, specifically at the Grin2b promoter in developing PFC with the chromatin immunoprecipitation assay. We expect enrichment of these repressor proteins at

the Grin2b promoter is at the core of NR2B dysfunction in this neurodevelopmental model for SCZ.

Disclosures: **Y. Gulchina:** None. **M.A. Snyder:** None. **W. Gao:** None.

Poster

771. Psychosis: Biochemistry

Location: Hall A

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Program#/Poster#: 771.15/E30

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: ZO1#HD000711-22

Title: A negative feedback loop controls NMDA receptor function in cortical interneurons via Neuregulin 2/ErbB4 signaling

Authors: ***D. VULLHORST**[1], R. M. MITCHELL[1], C. KEATING[1], S. ROYCHOWDHURY[1], I. KARAVANOVA[1], J.-H. TAO-CHENG[2], A. BUONANNO[1];
[1]Section on Mol. Neurobio., NICHD, NIH, Bethesda, MD; [2]EM Facility, Natl. Inst. of Neurolog. Disorders and Stroke, Bethesda, MD

Abstract: The Neuregulin receptor ErbB4 is an important modulator of GABAergic interneurons and neural network synchronization. However, little is known about the endogenous ligands that engage ErbB4, the neural processes that activate them or their direct downstream targets. Here we demonstrate that the NMDA receptor is both effector and target of Neuregulin 2 (NRG2)/ErbB4 signaling in cortical interneurons. We use double immunofluorescence in-situ hybridization and newly generated mouse and rabbit monoclonal antibodies to show that interneurons co-express ErbB4 and NRG2, and that NRG2 accumulates as an unprocessed pro-form on cell bodies atop subsurface cisterns. Evidence based on post-fixation immunofluorescence cytochemistry, live-cell imaging and Western blotting analysis of NRG2 protein demonstrates that NMDA receptor activation rapidly triggers shedding of the signaling-competent NRG2 extracellular domain. Unexpectedly, a proteomics analysis of proteins that associate with ErbB4 upon activation by NRG2 revealed GluN2B-containing NMDA receptors themselves as targets of NRG2/ErbB4 signaling. Electrophysiological recordings of whole-cell currents in cultured hippocampal neurons and of synaptically evoked EPSCs in acute PFC slices show that NRG2 rapidly and potently down-regulates NMDA, but not AMPA, receptor currents. These effects are mediated directly on ErbB4-positive GABAergic interneurons, and are not observed in ErbB4-negative pyramidal neurons. Our findings reveal an intimate reciprocal

relationship between ErbB4 and NMDA receptors with possible implications for the modulation of cortical microcircuits associated with cognitive deficits in psychiatric disorders.

Disclosures: D. Vullhorst: None. **R.M. Mitchell:** None. **C. Keating:** None. **S. Roychowdhury:** None. **I. Karavanova:** None. **J. Tao-Cheng:** None. **A. Buonanno:** None.

Poster

771. Psychosis: Biochemistry

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 771.16/E31

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: NIH-NIMH RO1MH66123 (RCR)

NIH-NIMH F31MH098566 (LAM)

Title: Tyrosine hydroxylase, GAD67, vGLUT1, and vGLUT2 proteins in the substantia nigra/ventral tegmental area in schizophrenia

Authors: *K. E. SCHOONOVER[1], L. A. MCCOLLUM[2], R. C. ROBERTS[2];
[1]Psychology and Behavioral Neurosci., [2]Psychiatry and Behavioral Neurobio., Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: Schizophrenia (SZ) is a serious mental illness with positive, negative, and cognitive symptoms. The substantia nigra/ventral tegmental area (SN/VTA) provides the largest dopaminergic (DA) input to the brain, and projects to the striatum that is the primary locus of action for antipsychotic drugs (APDs). The SN also receives both GABAergic and glutamatergic inputs that regulate neuronal activity. This study compared tyrosine hydroxylase (TH), glutamate decarboxylase (GAD67), and vesicular glutamate transporters (vGLUT1 and vGLUT2) in control and SZ postmortem human SN/VTA. The SZ cohort is tested as a whole and then divided by treatment status or treatment response. Postmortem caudal SN was obtained from the Maryland Brain collection. SZ (n=13) cases were compared to matched controls (NC, n=12). The SZ group was then subdivided by treatment status: no APD (SZ-Off, n=4 or on APD (SZ-On, n=9); or treatment response: treatment resistant (TR, n=5) and treatment responsive (RESP, n=4). Western blot analysis was used to measure protein levels of vGLUT1, vGLUT2, TH, GAD67, and actin. Optical density values were normalized to actin and the average NC value. NC vs. SZ: SZ had higher levels of TH compared to NC ($p = 0.01$), with a similar result for GAD67 ($p = 0.004$). vGLUT1 and vGLUT2 protein levels did not significantly differ between

the NC and SZ groups. NC, SZ-on, SZ-off: An ANOVA showed between group differences for TH, GAD67, and vGLUT2. TH protein levels were higher in SZ-on compared to NC ($p = 0.008$). GAD67 protein levels were also higher in SZ-on compared to NC ($p = 0.003$). In contrast, SZ-off had higher levels than NC ($p = 0.041$), with no difference between SZ-on and NC. Protein levels of vGLUT1 did not significantly differ, but showed a similar pattern to that of vGLUT2. NC, TR, RESP: An ANOVA showed between group differences for TH and GAD67. TR had significantly higher TH levels than NC ($p = 0.001$) and SZ-off ($p = 0.045$). Similarly, GAD67 levels in TR were significantly higher than NC ($p = 0.004$). No significant differences among groups were observed for vGLUT1 or vGLUT2. In summary, TH and GAD67 protein levels were increased in the caudal SN in SZ compared to controls, which could possibly be an APD effect; TR had higher levels of TH and GAD67 than NCs. vGLUT1 tended to be higher in SZ, especially in SZ-off, with no relationship to treatment response. vGLUT2 was increased in SZ-off, and had no relationship to treatment response. These data suggest abnormalities in DA and GABA transmission in SZ with a possible relation to treatment response. Glutamatergic inputs to the SN in SZ from subcortical regions (as marked by vGLUT2) may be elevated in SZ-off and normalized by APDs.

Disclosures: K.E. Schoonover: None. **L.A. McCollum:** None. **R.C. Roberts:** None.

Poster

771. Psychosis: Biochemistry

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 771.17/E32

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: Clozapine reduces Toll-like receptor 4/NF-κB-mediated inflammatory responses through Akt inhibition in microglia

Authors: *S. KIM[1], Y. KIM[2], S. SHIN[3];
[1]Dongguk Univ. Intl. Hosp., Ilsandong-Gu, Goyang-Si, Gyeonggi-Do, Korea, Republic of;
[2]Dongguk Univ., Gyeonggi-do, Korea, Republic of; [3]Konkuk Univ., Seoul, Korea, Republic of

Abstract: Clozapine (CZP) is an atypical antipsychotic agent used in the treatment of psychotic disorders including schizophrenia and bipolar disorder. Accumulating evidence suggests that neuroinflammation is closely associated with the pathogenesis of schizophrenia as well as bipolar disorders. In this study, we investigated the effect of CZP on anti-inflammatory activity in lipopolysaccharide (LPS)-stimulated microglia. CZP treatment suppressed LPS-induced phosphorylation of IkBα at Ser-32 and of p65/RelA at Ser-468, as well as NF-kB-dependent

transcriptional activity, as revealed by a cis-acting reporter assay system and analysis of NF-κB target gene expression. CZP downregulated LPS-induced Akt phosphorylation at Ser-473. Pharmacological Akt inhibitors ameliorated LPS-induced NF-kB activation, whereas ectopic expression of the constitutively active form of Akt (gag-Akt) abrogated the inhibitory effect of CZP on LPS-induced NF-kB phosphorylation. Removal of extracellular Ca2+ by EGTA or sequestration of intracellular Ca2+ by BAPTA-AM attenuated LPS-induced Akt phosphorylation. Treatment with calmodulin (CaM) antagonists and the CaM kinase inhibitor, KN-93, also prevented LPS-induced Akt and NF-κB activation. Ca2+/CaM-mediated Akt activation is critical in LPS-induced NF-κB activation in microglia. CaM antagonism by CZP plays an important role in anti-inflammatory activity through the inhibition of Akt-mediated NF-kB activation. The antipsychotic CZP could be a promising agent for prevention of TLR4-mediated neuroinflammation.

Disclosures: **S. Kim:** None. **Y. Kim:** None. **S. Shin:** None.

Poster

771. Psychosis: Biochemistry

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 771.18/E33

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: Rebecca L. Cooper Medical Research Foundation, PhD Scholarship.

Title: Cholinergic muscarinic receptor expression in post mortem brain tissue of schizophrenia patients

Authors: ***N. P. THOMAS**[1], E. SCARR[1], B. DEAN[2];
[1]Psychiatry, Univ. of Melbourne / Psychiatry, Parkville, Australia; [2]Mental Hlth., The Florey Inst. of Neurosci. and Mental Hlth., University of Melbourne, Australia

Abstract: Schizophrenia (SCZ) represents a complex mental health syndrome that likely represents a group of psychiatric conditions. A crucial step towards understanding the aetiology of SCZ, and developing better diagnosis and treatments is to identify potential subgroups within the diagnosis. This corresponds with a defined subgroup of schizophrenia subjects denoted muscarinic receptor deficient schizophrenia (MRDS). Making up 25% of the SCZ population, these subjects are separated due to their marked loss (75%) in cortical [3H] pirenzepine binding (specifically binds M1 subclass of muscarinic receptors), measured in post-mortem brain tissue. It has also been previously demonstrated that within the caudate putamen (C.P) there is

significantly reduced [3H] pirenzepine (PZP) and [3H] 5,11-dihydro-11-(((2-(2-((dipropylamino)methyl)-1-piperidinyl)ethyl)amino)carbonyl)6H-pyrido(2,3-b)(1,4)-benzodiazepin-6-one methanesulfonate (AF-DX) (specifically binds the M2/ M4 subclasses) binding in SCZ. However, it is not known if the extent of binding decreases are predominately driven by MRDS subjects, as they are in the cortex, regarding [3H]PZP. Therefore, in order to better understand the changes in muscarinic receptors in the C.P from subjects with SCZ, and to delineate whether the MRDS subgroup were identifiable by a marked loss of [3H]PZP in the sub-cortical region, we measured [3H]PZP and [3H]AD-FX-384 binding to C.P from 40 SCZ subjects, 20 of which were MRDS, and 20 non-psychiatric controls. Results:The level of [3H]PZP binding was significantly lower in the C.P from subjects with SCZ to CTRL ($p < 0.004$). There was significant variance in [3H]PZP binding when comparing MRDS, other SCZ subjects, and CTRL ($p < 0.001$), shown to be due to the lower levels of binding to C.P from subjects with MRDS compared to controls (p 0.0001). There was no significant difference between other SCZ subjects and CTRL. The level of [3H]AF-DX binding was significantly lower in the C.P from subjects with SCZ to CTRL ($p = 0.003$). There was significant variance in [3H]AF-DX-384 binding when comparing MRDS, other SCZ subjects, and CTRL ($p < 0.001$), shown to be due to the lower levels of binding to C.P from subjects with MRDS compared to controls (p 0.0001). There was no significant difference between other SCZ subjects and CTRL. Conclusions: Lower binding levels of [3H]PZP and [3H]AF-DX-384, indicative of M1 and M2/4 receptors respectively, within the C.P from subjects with SCZ are predominately driven by MRDS subjects, defined by their loss of cortical M1 muscarinic receptors. Support supplied by Rebecca L. Cooper Medical Research Foundation, PhD Scholarship.

Disclosures: **N.P. Thomas:** None. **E. Scarr:** None. **B. Dean:** None.

Poster

771. Psychosis: Biochemistry

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 771.19/E34

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: Lloyd Huck Graduate Research Dissertation Award

Title: Investigating the role of the schizophrenia risk gene ZNF804a in early brain development

Authors: ***Y. ZHOU**[1,2], F. DONG[1], X. JIANG[1], C. MCSWEENEY[1,2], Y. MAO[1,2];
[1]Penn State University, Biol. Dept., State College, PA; [2]Huck Inst. of the Life Sci., State college, PA

Abstract: ZNF804a was the first gene to reach genome-wide significance for psychosis when SNP rs1344706 was shown to be significantly associated combining SZ and bipolar disorder diagnoses. Several follow up genome-wide associated studies (GWAS) have replicated the association of rs1344706 with SZ and other psychosis in different populations. Although the association with SZ has been reported since 2008, the molecular function of ZNF804a remains unclear. We found that ZNF804a expression is high in the embryonic brain but decreased in the adulthood and ZNF804a localizes in both nucleus and dendrites. We performed *in utero* electroporation using B6 wild type mice on embryonic day 15 (E15) and transfected the neuronal progenitor cells with ZNF804a overexpression (OE) and knockdown (KD) constructs, both were tagged with GFP. On E18, the electroporated embryos were collected and the brains were processed with cryo-sectioning and fluorescent immunocytochemistry (ICC) staining. Quantitated results of GFP positive neuron showed overexpressing ZNF804a *in utero* significantly increased the migration of new born neuron, while knockdown endogenous ZNF804a significantly decreased the neuronal migration. To determine how ZNF804a regulates neuronal migration, we conducted the yeast two hybrid screen and identified novel proteins that interact with ZNF804a. Taken together, our study paved the road of understanding the molecular mechanism of ZNF804a and demonstrated its significant role for major mental illness in neuronal development.

Disclosures: **Y. Zhou:** None. **F. Dong:** None. **X. Jiang:** None. **C. McSweeney:** None. **Y. Mao:** None.

Poster

771. Psychosis: Biochemistry

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Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: NIH Grant 1R21NS089080

NIH Grant 1F31NS087713-01

Title: Regulation of AMPAR subunits by miR-137 and neuregulin: Implications for schizophrenia

Authors: ***K. THOMAS**[1], B. ANDERSON[1], D. HAWKINS[1], Q. GU[1], N. SHAH[1], G. BASSELL[1,2];
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Abstract: Schizophrenia is a debilitating cognitive disorder that affects approximately 1% of the world's population yet has no cure, no known cause, and no means of prevention. In 2011 a schizophrenia genome wide association study (GWAS) identified a patient-associated single nucleotide polymorphism near the gene for the microRNA (miRNA) miR-137. miRNAs are small noncoding RNAs that inhibit protein synthesis by silencing translation and/or promoting degradation of target mRNAs, which the miRNAs bind via complementary base pairing. Recent studies suggest that miR-137 plays a pivotal role in neuronal development and function, and many of its predicted and/or validated targets are also schizophrenia-associated risk loci. In the present study, we focus on the relationship between miR-137, neuregulin-1 (Nrg), and the AMPA receptor subunits GluA1 and GluA2, all of which are associated with schizophrenia susceptibility. Luciferase assay experiments suggest that miR-137 directly regulates GluA1 levels, and western blot experiments confirm that miR-137 regulates GluA1 and GluA2 levels in primary cortical neuron cultures. Additional luciferase assay experiments indicate that Nrg stimulation increases the activity of a firefly luciferase Gria1-3'UTR reporter. Acute stimulation of neuronal cultures with a soluble form of Nrg also leads to upregulation of GluA1 and GluA2. Fluorescence *in situ* hybridization experiments confirm that miR-137 localizes to the dendrites of primary cortical neurons but that dendritic levels are unchanged by acute Nrg stimulation. However, Nrg may regulate interactions between miR-137 and the RNA-induced silencing complex (RISC) component Ago2. Mutation of a predicted miR-137 binding site ablates the effect of Nrg, indicating that Nrg may regulate GluA1 through a miR-137-dependent mechanism. We propose that Nrg stimulation causes RISC to release miR-137, allowing the translation of Gria1 mRNA and production of new GluA1 protein. Nrg may regulate GluA2 by a similar mechanism or through a GluA1-dependent mechanism. Together these data elucidate a novel schizophrenia-associated translational control pathway and provide a basis for future studies examining how Nrg regulates miRNA activity and the functional consequences of this AMPAR subunit upregulation.

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Poster

771. Psychosis: Biochemistry

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 771.21/E36

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: NIH R01MH094358

Title: The value of interleukin 6 as a peripheral diagnostic marker in schizophrenia

Authors: *K. A. CHASE[1,2], J. J. CONE[3], C. ROSEN[1], R. P. SHARMA[1,4];
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Abstract: Background: Patients with schizophrenia have alterations in immune system functioning. This, coupled with studies indicating the impact of maternal illness on offspring development, strongly implicate associations between the inflammasome and schizophrenia. As such, the dynamic and complicated protein interleukin 6 (IL-6), both a pro- and anti-inflammatory cytokine, has been examined for its role in the development, course, symptomology, and applicability as a biomarker of schizophrenia. IL-6 and sIL-6R serum levels are significantly elevated in patients with schizophrenia, with implications on symptom severity. Methods: In this study, we examined IL-6 mRNA levels by real-time RT-PCR from fresh extracted peripheral blood mononuclear cells (PBMC) in 106 participants, including 53 patients with schizophrenia and 53 healthy individuals. Changes in mRNA expression were measured using qRT-PCR with β-Actin and GAPDH for normalization. Results: We found that peripheral PBMC IL-6 mRNA levels could function as a predictor of a diagnosis of schizophrenia. Furthermore, in participants with schizophrenia, we also found elevated levels of IL-6 mRNA with earlier ages of illness onset and worse positive symptom presentation, as measured by the Positive and Negative Syndrome Scale. Discussion: These findings provide important and continued support for a pathophysiological role for inflammation in patients with schizophrenia. Future utilization of peripheral IL-6 mRNA levels could potentially function as yet another tool in a clinician's tool belt during an initial diagnosis and tailoring of individualized treatment plans for patients with schizophrenia. Conclusions: Associations between a pro-inflammatory state and schizophrenia have been one of the more enduring findings of psychiatry, with various lines of evidence suggesting a compelling role for IL-6 in the underlying pathogenesis of schizophrenia.
Grant Support: This work was supported in part by PHS grant (NIH) R01MH094358 (RPS).

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Poster

771. Psychosis: Biochemistry

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Program#/Poster#: 771.22/E37

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: The protein-protein interaction landscape of Schizophrenia

Authors: B. WILKINSON[1], J. LI[1], H. YANG[1], W. ZHANG[2], F. SUN[2], K. WANG[1,3], *M. P. COBA[1,3];
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Abstract: Recent technological advances in large-scale human genetics has ben able to start to unveil the genetic architecture of schizophrenia (SCZ). While the identification of a variety of risk factors suggests a broad convergence in developmental, glutamatergic, and postsynaptic density (PSD) pathways, it is not clear if these sets of molecules associates in common signaling mechanisms at different developmental stages and subcellular localization. Here, using immunopurification and proteomics assays, we identified the spatial and temporal context where common and rare SCZ risk factors are associated. We determined 3360 in-vivo protein-protein interactions across 36 protein complexes and defined major clusters for enrichment of SCZ risk factors at mouse embryonic day 14 (e14) and adult PSD. Mutations in SCZ risk factors modifies the composition of these protein complexes trough protein domain interactions regulated by protein domains/ligand phosphorylation, and cluster a discrete number of protein domains defining molecular functions. These results were integrated into a software platform: Psychiatric Protein/Pathways Resource (PsyPPRes) that allows to prioritize SCZ candidate risk factors and place them within their molecular context.

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Poster

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Program#/Poster#: 771.23/E38

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: (NIH) R01MH094358

Title: Histone phosphorylation in schizophrenia and normal subjects; at the end of the cascade

Authors: R. P. SHARMA[1,2], B. FEINER[1], *J. K. MELBOURNE[1], K. A. CHASE[1,3];
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Abstract: Background: Histone modifications in peripheral blood cells are susceptible to multiple epigenetically active bio-chemicals in circulation. These organic molecules, which include all drugs of abuse and most psychotropic drugs, can activate kinase phosphorylation signaling cascades that penetrate to the level of nuclear chromatin and act directly on the histone H3 tail at the Serine 10 position. Methods: Peripheral blood cells (PBMC) from normal controls (n=42) and subjects with schizophrenia (n=37) were extracted using the Ficoll method. Participants with schizophrenia were diagnosed using the SCID and clinical measures obtained include symptom inventories (PANSS) and overall social functioning (Heinrichs-Carpenter scale). H3S10phos histone modification levels were measured in acid histone extracts of PBMC, using a commercially available ELISA assay. Results: Participants with schizophrenia had a significant and approximately 50% increase in average levels of H3S10phos in their peripheral blood cells when compared to normal controls. Increased levels of H3S10phos were associated with several dimensions of the PANSS and the Heinrichs-Carpenter, both indicating improved symptom presentation and quality of life. Conclusions: These results encourage further characterization of peripheral blood levels of histone modifications to facilitate epigenetic research in living patients. It also suggests that kinase cascades, emanating from membrane receptors, maybe an alternate approach to opening restrictive chromatin with the objective of improved genomic response to therapeutics.

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Poster

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Topic: C.15. Schizophrenia and Bi-polar Disorder

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EU-FP7 (MC-ITN “IN-SENS” #607616)

Title: Domain analysis of TRIOBP-1 implies a common basis underlying its actin polymerization activity and its aggregation in schizophrenia

Authors: *N. J. BRADSHAW, R. MARREIROS, C. KORTH;
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Abstract: The presence of aggregates of specific proteins in the brain can be used to characterize multiple neurodegenerative conditions, and arises as a result of imbalances in protein homeostasis during the development of the condition. We have previously proposed that similar protein deposits may arise in subsets of patients suffering from chronic mental illness, and were able to determine that proteins produced by two established schizophrenia risk factors, DISC1 and dysbindin, could be seen to aggregate specifically in the brains of a subset of patients with major mental illness. To detect other such proteins not previously implicated by genetics, we employed an antibody proteomics approach, identifying TRIOBP-1 as an additional protein which putatively shows schizophrenia-specific aggregation in the brain. The propensity for both over-expressed and endogenous TRIOBP-1 protein to aggregate was then confirmed in a variety of systems. The TRIOBP-1 protein is predicted to consist of an N-terminal Pleckstrin homology domain, as well as extensive predicted coiled-coil regions. In order to investigate the domain structure of TRIOBP-1 in more depth, and specifically in order to determine which elements of the protein were implicated in both its normal function and in its aggregation propensity, a large number of constructs were subcloned containing combinations of structural elements of TRIOBP-1. These were expressed in both neuroblastoma cell lines and in E. coli for recombinant protein production. In this manner, we have now identified a central segment of the protein, as being critical for the aggregation of the coiled-coil C-terminal segment of TRIOBP-1. The N-terminal section of TRIOBP-1 shows no such propensity, but was seen to be localized to the actin cytoskeleton by this same central region, implying a common underlying relationship between the aggregation and actin-binding features of TRIOBP-1. We have also found the first evidence that the N- and C-terminal portions of TRIOBP-1 may play distinct roles in the promotion of actin polymerization by TRIOBP-1. Experiments to confirm the relevance of TRIOBP-1 aggregation to schizophrenia in the wider population are currently underway. Through probing a protein misfolding event seemingly present in at least a subset of patients, we hope to determine both its potential utility as a biomarker, and more generally to understand a physiological element of chronic mental illness which has the potential to lie downstream of both genetic and environmental risk factors.

Disclosures: N.J. Bradshaw: None. **R. Marreiros:** None. **C. Korth:** None.

Poster

771. Psychosis: Biochemistry

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Program#/Poster#: 771.25/E40

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: *In vivo* biochemical studies with xanomeline emphasize the importance of the M4 subtype of muscarinic receptors

Authors: *M. POPIOLEK, J. HARMS, S. GRIMWOOD;
Neurosci. Res. Unit, Pfizer, Cambridge, MA

Abstract: Preclinical and clinical studies suggest that muscarinic receptor (mAChR) activation may be therapeutically beneficial for the treatment of schizophrenia and Alzheimer's disease. This is best exemplified by work with xanomeline, whose efficacy is thought to be via co-activation of M1 mAChRs, which are Gαq-coupled, and M4 mAChRs, which are Gαi-coupled. *In vivo* biochemical studies were performed to investigate the effect of xanomeline on intracellular signaling cascades in the mouse brain. Phosphorylated 3'-5'-cyclic adenosine monophosphate (cAMP)-response element binding protein (pCREB) was measured as an indicator of M4 activity due to preferential expression of M4 mAChRs on the striatal D1 expressing medium spiny neurons of the direct pathway, as well as the modulatory role they play in mediating signaling in these cells. Administration of 3.2 mg/kg xanomeline (15 min, s.c.) significantly decreased (~25%) striatal pCREB levels, relative to vehicle-treated controls. This effect was blocked by the M4-preferring mAChR antagonist tropicamide (10 mg/kg i.p; 20 min), but not by the M1-preferring mAChR antagonist VU-0255035 (32 mg/kg i.p.; 30 min). Similar decreases in striatal pCREB levels observed with xanomeline treatment were also shown for the M4-selective PAM, PT-3763 (3.2 mg/kg s.c.; 15 min). Effects by xanomeline and PT-3763 on pCREB were not, however, robustly apparent in either the hippocampus or prefrontal cortex. These data suggest that xanomeline mediates striatal pCREB effects through the M4 subtype of mAChRs.

Disclosures: **M. Popiolek:** None. **J. Harms:** None. **S. Grimwood:** None.

Poster

771. Psychosis: Biochemistry

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Topic: C.15. Schizophrenia and Bi-polar Disorder

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Drunken Moon Lake Integrated Scientific Research Platform and Aim for Top University Project from National Taiwan University

Title: The effect of lithium on the alleviation of AKT1-related neuromorphological and behavioral deficits in P19 cell line, primary cell culture, and Akt1 mutant mice

Authors: *C.-Y. CHANG[1], D.-Z. LUO[2], T.-W. WANG[5], V. STUDER[6], W.-S. LAI[2,3,4]; [2]Psychology, [3]Grad. Inst. of Brain and Mind Sci., [4]Neurobio. and Cognitive Sci. Ctr., [1]Natl. Taiwan Univ., Taipei, Taiwan; [5]Life Sci., Natl. Taiwan Normal Univ., Taipei, Taiwan; [6]Interdisciplinary institute for Neurosci., Univ. Bordeaux, Bordeaux, France

Abstract: Schizophrenia is a severe neuropsychiatric disorder that is hypothesized to result from genetic predisposition and disturbances in early brain development. Accumulating evidence from human genetic and animal studies suggests that AKT1 is a susceptible gene for schizophrenia. Emerging evidence indicates that a sex-specific role of Akt1 in the modulation of methamphetamine induced hyperlocomotion, depression-like behavior, sensorimotor gating function, and neuromorphology. Our recent study also revealed that Akt1-deficit mice are insensitive to antipsychotic drugs, but glycogen synthase kinase 3 (GSK3, a key downstream kinase for Akt1) inhibitor might have therapeutic potential. Given the fact that lithium is a GSK3 inhibitor and a mood-stabilizing drug for the treatment of bipolar disorder, it is of great interest to evaluate the therapeutic potential of lithium on the alleviation of Akt1-related neuromorphological and behavioral deficits. Taking advantage of P19 embryonal carcinoma cells, rat hippocampal primary cell culture, and Akt1 heterozygous mutant (Akt1+/-) mice as our models, a series of experiments was conducted *in vitro* and *in vivo*. First, using Ascl1 to differentiate P19 embryonal carcinoma cells into neurons, we examined the effect of AKT1/2 inhibitor on the neuromorphological alterations in DIV3 and the rescue effect of lithium. Quantitative analyses of Tuj1-immunostained P19-driven neurons revealed that AKT1/2 inhibitor resulted in a 60% reduction of neurite length but no difference was found in the number of differentiated neurons. But the reduction of neurite outgrowth can be rescued by the treatment of Lithium (0.5 & 1 mM). In hippocampal primary cell culture, a similar (60%) reduction in neurite length was observed in DIV3 as well. And such reduction can be alleviated by the optimal dose of lithium (8 & 10 mM) treatment. Based on these results and our previous findings, a set of 3 behavioral tasks was performed in Akt1+/- female mice and their wild-type littermate controls after chronic administration of lithium (100 mg/kg, i.p., twice per day) or saline. Compared to WT controls, chronic treatment of lithium alleviated observed behavioral impairments in Akt1+/- mice, especially in the tail suspension task and acoustic PPI. The treatment of lithium also dampened methamphetamine-induced stereotypic behaviors in both groups compared to their saline controls. Collectively, out findings suggest the therapeutic potential of lithium for the treatment of schizophrenia and the importance of GSK3 as a new therapeutic target.

Disclosures: **C. Chang:** None. **D. Luo:** None. **T. Wang:** None. **V. Studer:** None. **W. Lai:** None.

Poster

771. Psychosis: Biochemistry

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Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: Marie Curie FP7-PEOPLE-2013-ITN IN-SENS network

Title: Electrophysiological characterization of tgDISC1 rats: a preclinical model of DISC1opathies

Authors: ***M. VENZI**[1,2], S. TROSSBACH[3], R. MARREIROS[3], C. KORTH[3], N. BRANDON[4], E. ÅBERG[1,2];
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Abstract: DIsrupted in SChizophrenia 1 (DISC1) is a gene originally associated to chronic mental diseases (CMD) (schizophrenia, depression and bipolar disorder) in a Scottish pedigree. Since then, a wealth of genetic and biological data have further strengthened the association between DISC1 and CMD (Brandon and Sawa, 2011). Importantly, alterations in DISC1 have also been independently found in a subgroup of CMD patients from the Stanley Medical Research Institute Consortium Collection (Leliveld et al. 2008). Insoluble aggregates of DISC1 protein were identified in the post-mortem brain tissue of these patients; this finding, coupled with molecular evidence of the cell-invasiveness of DISC1, suggests that a group of DISC1 dependent brain disorders could be clustered together as protein conformational disorders, or 'DISC1opathies' (Korth, 2012). To further investigate DISC1opathies, a rat line mildly overexpressing human DISC1 under the PrP promoter was recently generated (Korth, et al.). The tgDISC1 line is characterized by: 1) DISC1 aggregates in medial prefrontal cortex and striatum 2) behavioral phenotypes such as aphetamine hypersensitivity and hyperexploratory behavior 3) a molecular phenotype of striatal dopaminergic dysfunction (e.g., an increase in the proportion of dopamine D2 receptors in the high affinity state). To characterize the electrophysiological phenotype(s) of the tgDISC1 rats, ongoing experiments are being carried out with tgDISC1 (n=8) and wild-type littermates (n=8) implanted with fronto-parietal EEG and EMG electrodes; the animals will be recorded monthly with a telemetry system between 3 and 12 months. Here we

will present preliminary longitudinal data on the tgDISC1 animals describing alterations in sleep architecture, sleep spindles and EEG power spectra. In parallel, brain aggregates in tgDISC1 rats will be measured semi-quantitatively via western blotting in independent groups of animals at 3 and 6 months. Finally, we will present preliminary extracellular ensemble recordings performed in tgDISC1 freely moving animals with silicon probes implanted in the dorsal striatum. Funding: INSENS network Marie Curie FP7-PEOPLE-2013-ITN IN-SENS network Brandon NJ, Sawa A. Nat. Rev. Neurosci. 2011;12:707-22. Leliveld SR, et al. J. Neurosci. 2008;28:3839-45. Korth C. Prion. 2012;6:134-41.

Disclosures: **M. Venzi:** A. Employment/Salary (full or part-time):; AstraZeneca. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; INSENS network Marie Curie FP7-PEOPLE-2013-ITN IN-SENS network. **S. Trossbach:** None. **R. Marreiros:** None. **C. Korth:** None. **N. Brandon:** A. Employment/Salary (full or part-time):; AstraZeneca. **E. Åberg:** A. Employment/Salary (full or part-time):; AstraZeneca.

Poster

772. Schizophrenia: Antipsychotics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 772.01/E43

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: Rat models of schizophrenia using NMDA antagonist Dizocilpine

Authors: *Q. CHANG, W. LACSINA, C. N. COHRON, T. HANANIA;
PsychoGenics Inc., Montvale, NJ

Abstract: Studies have shown that animals models involved in glutamatergic pathways are important tools to study negative and cognitive symptoms of schizophrenia. NMDA receptor antagonist dizocilpine (MK-801) elicit schizophrenia-like symptoms in humans and in animal models. In the present studies, we assessed the effects of acute administrations of MK-801 on recognition memory and executive function. We also tested the efficacies of memory enhancer galantamine, antipsychotics olanzapine and clozapine, as well as selective 5-HT2A receptor antagonist volinanserin (MDL100907) in reversing the MK-801 induced deficits. Subjects were exposed to acute MK-801 (0.15 mg/kg) 30 min. prior to behavioral tests. For serial reversal learning (RVL) test, subjects had been sufficiently trained and acquired the tasks prior to MK-801 exposure. For novel object recognition (NOR) test, rats were naïve to testing prior to MK-

801. In both assays, MK-801 provided deficit models in order to assess efficacies of compounds. The results indicated that MK-801 treatments induced impairments in recognition memory in NOR test and deficits in executive function in RVL test. Administration of acetylcholinesterase (AChE) inhibitor galantamine (1 mg/kg) significantly saved impairment of recognition memory in NOR test. In RVL test, olanzapine (0.3 and 1 mg/kg), clozapine (3 mg/kg) and MDL 100907 (1 mg/kg) all showed efficacy in saving reversal learning deficit caused by MK-801 treatment. These studies provide examples of memory impairment and treatment in animal models of schizophrenia, and demonstrated that deficit of executive function shown in animal models of schizophrenia are sensitive to the atypical antipsychotic clozapine and olanzapine. These results, together with our results obtained (and reported) earlier from rat models of schizophrenia using phencyclidine (PCP), are likely relevant to the cognitive impairments and negative symptoms (such as impaired social functioning shown in PCP models) of schizophrenia. Therefore these animal models can provide useful tools for the evaluation of novel antipsychotics.

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Poster

772. Schizophrenia: Antipsychotics

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Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: ISF-2092-14

Title: Risperidone prevents gender-sensitive depression of hippocampal excitatory transmission in a rat model of schizophrenia

Authors: ***A. S. PERETZ**[1], E. PATRICH[1], Y. PIONTKEWITZ[1], I. WEINER[2], B. ATTALI[2]; [1]Physiol., Sackler Sch. of Med. / Tel Aviv Univ., Tel Aviv-Yafo, Israel; [2]Tel Aviv Univ., Tel Aviv-Yafo, Israel

Abstract: Schizophrenia is associated with behavioral and brain structural abnormalities, of which the hippocampus appears to be one of the most consistent region affected. Electrophysiological studies performed on the poly I:C model of schizophrenia suggest that alterations in hippocampal synaptic transmission and plasticity take place in the offspring. However, these investigations yielded conflicting results and the neurophysiological alterations responsible for these deficits are still unclear. Here we performed for the first time a longitudinal study examining the impact of prenatal poly I:C treatment and of gender on hippocampal

excitatory neurotransmission. In addition, we examined the potential preventive/curative effects of risperidone (RIS) treatment during the peri-adolescence period. Excitatory synaptic transmission was determined by stimulating Schaffer collaterals and monitoring fiber volley amplitude and slope of field-EPSP (fEPSP) in CA1 pyramidal neurons in male and female offspring hippocampal slices from postnatal days (PNDs) 18-20, 34, 70 and 90. Depression of hippocampal excitatory transmission appeared at juvenile age in male offspring of the poly I:C group, while it expressed with a delay in female, manifesting at adulthood. In addition, a reduced hippocampal size was found in both adult male and female offspring of poly I:C treated dams. Treatment with RIS at the peri-adolescence period fully restored in males but partly repaired in females these deficiencies. A developmental and sex dependent decrease in hippocampal excitatory transmission occurs in the offspring of poly I:C treated pregnant mothers. Pharmacological intervention with RIS during the peri-adolescence period can cure in a gender-sensitive fashion early occurring hippocampal synaptic deficits.

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Poster

772. Schizophrenia: Antipsychotics

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Topic: C.19. Drug Discovery and Development

Support: NIH Grant R01 MH093450-03

Title: Developing translatable biomarkers of schizophrenia: assessment of three NMDA receptor antagonist-based pharmacological mouse models of schizophrenia using the auditory steady state response (ASSR)

Authors: *K. A. RICHARDSON[1], E. BUERGER[1], Y. HIRANO[2,3], K. SPENCER[2], D. GERBER[1], M. LEVIN[1];
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Abstract: Cognitive impairments associated with mental illness remain a major area of unmet medical need. One factor contributing to the difficulty in discovering effective CNS therapeutics is the absence of reliable translational biomarkers for use as objective measures of drug efficacy. Synchronized neural oscillations, which are conserved across species, are associated with distinct

cognitive functions in certain frequency ranges (e.g. gamma: 30-100 Hz), and abnormalities in particular oscillations have been observed in various neuropsychiatric disorders. For example, deficits in gamma oscillations in schizophrenia patients have been demonstrated using auditory steady state response (ASSR) (Spencer et al. Biol Psychiatry 2008, Spencer et al. BMC Neuroscience 2009). Recent results have suggested that this alteration in gamma activity is not confined to auditory evoked potentials, but is also reflected in spontaneous power (Hirano et al. JAMA Psychiatry 2015). ASSR phase-locking factor (PLF) was found to be decreased at 40 Hz stimulation whereas induced power during stimulation and between stimuli (baseline) was increased across the gamma band in patients relative to healthy controls. Here we examined 3 glutamatergic, pharmacological mouse models of schizophrenia (PCP, Ketamine and MK-801; administered IP) using ASSR. Male C57BL/6 mice were implanted with microwire tungsten bundles placed in primary auditory cortex. Local field potentials (LFP) were recorded during presentation of click trains of various frequencies (20-100 Hz). Evoked power in the LFP was increased at lower frequencies of stimulation (20-50 Hz) in all three models. At higher stimulation frequencies, the observed effects depended on the model: PCP increased evoked power, Ketamine decreased evoked power and MK-801 had no effect on evoked power. Phase-locking at 20 Hz was generally increased in all 3 models. These results are in contrast to the observed decreases in evoked power and PLF at 40 Hz in the human disease condition. Analysis of induced power in the mouse models, however, showed alterations in power similar to those observed in patients. During the baseline period (between stimuli), induced power in all three models was increased in the gamma band (30-100 Hz). During the stimulus period, induced power in the gamma band in PCP and Ketamine models was also increased. In summary, we find that the NMDA receptor antagonist-based pharmacological models of schizophrenia recapitulate only a subset of electrophysiological findings in human schizophrenia patients as assessed with ASSR.

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Poster

772. Schizophrenia: Antipsychotics

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Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: FAPERJ

CNPq

IOC/FIOCRUZ

PROEP

Title: Effect of resveratrol on schizophrenia-like behavior induced by immunogenic challenger by poly(I:C) during pregnancy

Authors: *F. R. FERREIRA[1], T. R. P. POMBO[2], V. P. L. GONÇALVES[2], R. L. FROZZA[1], S. S. GUTERRES[3], A. R. POHLMANN[3];
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Abstract: Schizophrenia (SZ) is considered a neurodevelopmental disorder with important genetic component. Some authors suggest that, at least in a subgroup of patients, SZ might be caused by congenital alterations induced by environmental factors, particularly infections by some microorganisms. Despite clear evidences showing that maternal infection and maternal immune activation increases risks for SZ and autism, the mechanisms involved still are fully unknown. On the other hand, resveratrol (3,4',5-trihydroxy-trans-stilbene), a natural non-flavonoid polyphenol with antioxidant and anti-inflammatory activity, has shown protective effects against a number of cardiovascular and neurodegenerative diseases. The potential of resveratrol as protective agent to inflammatory insults during pregnancy still remains to be investigated. Here, we are using prenatal stimuli with poly(I:C)(=polyriboinosinic-polyribocytidilic acid), an established infection-based model, to investigate whether the treatment with resveratrol prevents the congenital SZ-like behavior. Pregnant mice received six doses of microencapsulated resveratrol (3,6 mg/Kg, i.p., per day, starting at E6) or empty microcapsules. The dams also were challenger once with poly(I:C) (30 mg/Kg), i.p., at E9, or saline. The behavioral impairments related to SZ to the pups were analyzed at day P61 using object recognition (OR) and social integration (SI) tests. There were no any effects to the poly(I:C) immunogenic challenge, resveratrol treatment or interaction for the pups when they were tested to OR. However, pups from dams stimulated with poly(I:C) showed reduction to the interaction time with unfamiliar mouse, when exposed together with a familiar mouse, at the SI test. Pups from dams stimulated with poly(I:C) and treated with resveratrol spent more time exploring unfamiliar mouse, when exposed together to a familiar mouse, an behavior similar to observed to the control group. These preliminary results suggest that treatment with resveratrol might prevent some of the SZ-like behavior at pups from dams exposed to infection. Therefore, the protective effect of resveratrol to congenital neurodevelopmental diseases might be broadly investigated.

Disclosures: F.R. Ferreira: None. **T.R.P. Pombo:** None. **V.P.L. Gonçalves:** None. **R.L. Frozza:** None. **S.S. Guterres:** None. **A.R. Pohlmann:** None.

Poster

772. Schizophrenia: Antipsychotics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 772.05/E47

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: University of St Andrews Doctoral Fellowship

Title: Reversal learning but not set-shifting deficits in the methylazoxymethanol acetate model of schizophrenia: a partial replication with implications for N-Methyl-D-aspartate receptor treatment for cognitive deficits in schizophrenia

Authors: *A. J. WHYTE, T. SCHARBERT, D. O' HAGAN, H. MARSTON, D. S. TAIT, V. J. BROWN;
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Abstract: In rats, treatment with methylazoxymethanol acetate (MAM) on embryonic day 17 generates a model of schizophrenia, the phenotype of which includes ventricular enlargement, hippocampal (HIPP) and frontal cortex (FTX) pathologies, and behavioural deficits consistent with those found in patients with schizophrenia. To probe the effectiveness of N-Methyl-D-aspartate receptor (NMDAR) positive allosteric modulator ORG49209 in treating schizophrenia-related cognitive deficits, we obtained a cohort of MAM-treated rats (Sprague Dawley, Charles River) for testing in the attentional set-shifting task (ASST). The ASST measures executive functioning through a series of two-choice discriminations. Key measures in the ASST include the reversal stages and the extradimensional shift stage (ED), which requires the subject to respond to a previously irrelevant dimension. Patients with schizophrenia display increased trials to criterion (TTC) and errors, during reversal stages and the ED a finding also reported for MAM-treated rats in the rodent ASST, which uses digging medium and odour as discriminative dimensions. To confirm these previous findings in MAM-treated rats, we performed two baseline tests. In both the initial and the repeat baseline tests we found increased TTC and errors during the first reversal stage in MAM-treated rats compared to saline controls. However, neither test unveiled a set-shifting deficit in MAM-treated rats as they did not display elevated TTC during the ED compared to controls. We next examined the effect of ORG49209 on ASST performance using a Latin square design (0, 3, 10 mg/kg/ml). Treatment with ORG49209 abolished the reversal learning deficit by reducing TTC in MAM-treated rats and increasing TTC in saline controls, suggesting potential efficacy of ORG49209 in schizophrenia. Our anatomical and histological results revealed reductions in gross brain weight, enlargement of the lateral ventricles, FTX and HIPP microcephaly, and disruption of the CA2/CA3 cell layers in MAM-

treated rats compared to controls all consistent with previous reports. Reductions in parvalbumin positive (PV+) interneurons were evident in the dentate gyrus but not any other regions however, a result that is inconsistent with reports of reductions in PV+ interneurons throughout the FTX and HIPP. Despite the cohort of MAM-treated rats we examined only partially exhibiting the reported phenotype, our results with ORG49209 suggest that the underlying pathology in this cohort is responsive to enhancement of NMDAR activity a finding that is consistent with previous reports on schizophrenia-related cognitive deficits.

Disclosures: **A.J. Whyte:** None. **T. Scharbert:** None. **D. O' Hagan:** None. **H. Marston:** None. **D.S. Tait:** None. **V.J. Brown:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Eli Lilly. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Eli Lilly.

Poster

772. Schizophrenia: Antipsychotics

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Topic: C.19. Drug Discovery and Development

Support: NIH Grant R01MH99993

NIMH Grant 271201300017C-1-0-1

Title: Design and study of new 5-ht2c agonists for use in treating schizophrenia

Authors: *J. CHENG[1], R. M. RODRIGUIZ[2], P. M. GIGUERE[3], B. L. ROTH[3], W. C. WETSEL[2], A. P. KOZIKOWSKI[1];
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Abstract: Two highly selective serotonin 2C (5-HT2C) agonists (+)-JJ-3-42B and (+)-JJ-3-45B have been designed and tested for their ADME-Tox properties as well as their ability to work in animal models of schizophrenia-like behaviors. In the *in vitro* ADME-Tox tests, both compounds showed low plasma-protein binding, high Caco-2 and MDCK-MDR1 biomembrane

permeability, high microsomal stability, and excellent cytochrome P450 and hERG safety. Both compounds displayed no nephrotoxicity or neurotoxicity at a high concentration (150 μM) and both were negative in the Ames fluctuation test. Additionally, compound (+)-JJ-3-42B had a half-life of 1.8 h and a bioavailability (%F) of 53 in mice. Oral administration of (+)-JJ-3-42B to mice at a dose of 10 mg/kg provided a maximal brain concentration of 5.2 μg/g and a brain/plasma concentration ratio of greater than 10. Compounds (+)-JJ-3-42B and (+)-JJ-3-45B were examined in three behavioral tests. (a) In amphetamine-induced hyperlocomotion, both compounds significantly reduced the hyperactivity in mice at the doses of 10 mg/kg and 20 mg/kg, while 20 mg/kg (+)-JJ-3-42B normalized this response. (b) Amphetamine-disrupted prepulse inhibition (PPI) was rescued with compound (+)-JJ-3-42B in a dose range of 1-4 mg/kg, with 2 mg/kg showing the best efficacy. Additionally, (+)-JJ-3-45B also restored PPI at a 0.5-2 mg/kg dose range, with 0.5 mg/kg showing the highest efficacy. (c) In preliminary studies with the NR1 knockdown (NR1-KD) mice, both compounds (+)-JJ-3-42B and (+)-JJ-3-45B partially normalized object recognition memory at doses of 5 and 1 mg/kg, respectively. Together, the above ADMET and animal behavioral data support the further development of the selective serotonin 2C agonists, (+)-JJ-3-42B and (+)-JJ-3-45B, as potential anti-schizophrenic drugs.

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Poster

772. Schizophrenia: Antipsychotics

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Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: MH104320

Title: Prior D2 antagonist antipsychotic drug treatment prevents response to novel target compounds in MAM model of schizophrenia: potential circumvention using aripiprazole

Authors: *S. SONNENSCHEIN, K. M. GILL, S. A. MILLER, A. A. GRACE;
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Novel target compounds for the treatment of schizophrenia have shown promise preclinically, but failed to show efficacy in clinical trials, which has led some to conclude that results from preclinical studies do not translate to the human condition. However, there is an important difference: preclinical research is performed on drug naïve rats, whereas clinical trials

are performed on patients that have received only brief withdrawal from years of prior antipsychotic drug treatment despite potential pervasive changes to the DA system. We recently found that withdrawal from repeated haloperidol (HAL) treatment interferes with the ability of a novel target compound to reverse the hyperdopaminergic state and hippocampal hyperactivity in the methylazoxymethanol acetate (MAM) neurodevelopmental model of schizophrenia. In the current study, we examined whether this would also occur with other, mechanistically distinct, first and second-generation antipsychotic drugs, with a focus on the D2 partial agonist aripiprazole (ARI). Electrophysiological recordings were conducted from spontaneously active DA neurons in the ventral tegmental area of anesthetized normal rats following 7d withdrawal from repeated HAL (0.6 mg/kg), clozapine (CLO; 10 mg/kg), or ARI (10 mg/kg) treatment for 21 d, p.o. Compared to vehicle-treated animals, rats withdrawn from repeated HAL and CLO treatment demonstrated reduced spontaneous DA neuron activity, likely due to depolarization block. This effect was not observed following ARI withdrawal, in which there was no change in DA neuron activity. This provides preliminary evidence that, in contrast to HAL and CLO, ARI may not induce depolarization block in VTA DA neurons. Lack of evidence for depolarization block and/or DA supersensitivity following repeated ARI treatment would suggest that it may be an effective transitional drug to test novel potential antipsychotic drugs without requiring an extended withdrawal period.

Disclosures: S. Sonnenschein: None. **K.M. Gill:** None. **S.A. Miller:** None. **A.A. Grace:** None.

Poster

772. Schizophrenia: Antipsychotics

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Topic: C.19. Drug Discovery and Development

Title: Locomotor activity in zebrafish larvae as a behavioural screen for drugs targeting 5-HT_{2C} and/or melatonin receptors

Authors: N. RIBEIRO PALHA, *A. DEKEYNE, S. VEIGA, W. BOUCHERON, P. DELAGRANGE, C. LOUIS, P. LESTAGE;
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Abstract: Background. As an organism model at the interface between cellular-based assays and mammalian models, zebrafish (*Danio rerio*) is becoming increasingly popular for drug discovery processes. For instance, locomotor response to alternating periods of light and dark in zebrafish larvae has been proposed as a high-throughput *in vivo* screening test for efficacy/toxicity

assessment of neuroactive drugs (Ellis et al., 2012). However, few studies have been conducted to characterize *in vivo* mechanisms of action of potential new therapeutics. This work aimed at deciphering actions of prototypical serotonin (5-HT)$_{2C}$ and melatonin (MT) agonists/antagonists on larval locomotor response. Since orthologous genes to human 5-HT$_{2C}$ and MT receptor genes have been identified in zebrafish, specificity of action of agonists was also checked by use of morpholino-induced knockdown technology (Nasevicious & Ekker, 2000). Method**.** Five days post-fertilization wild-type larvae or morphants were individually placed in a 96-well microtiter plates, in E3 medium. Drug solutions prepared in DMSO were added to wells. Plates were then introduced in a tracking system (ZebraBox, ViewPoint). The total distance moved per light/dark cycle was recorded for 2 rounds of 10 min light + 14 min dark. After tracking, individual viability or morphological alterations were assessed, and gene silencing in morphants was checked by quantitative RT-PCR. Results**.** Control larvae displayed higher activity during dark *vs* light periods, a behavioural profile which is blocked by intermediate concentrations (3-10-30 µM) of the selective 5-HT$_{2C}$ agonist, Ro600175. This effect could not be related to sedation since higher concentration (100 µM) increased activity during light periods. Hypoactivity induced by Ro600175 (10 µM) was concentration-dependently reversed by selective 5-HT$_{2C}$ antagonists (SB242084, RS102221 and S32006) and was decreased in 5-HT$_{2C}$ morphants. Melatonin, MT antagonists (S20928 and luzindole) and the antidepressant, agomelatine, which possesses mixed 5-HT$_{2C}$ antagonist and MT agonist properties, all concentration-dependently decreased the activity during dark periods. Conclusion**.** Locomotor activity in zebrafish larvae may be proposed as a behavioural screen for "pure" 5-HT$_{2C}$ receptor antagonists, but not for melatonin agonists, nor for compounds endowed with additional MT agonist activity such as agomelatine-like drugs. In this latter case, blockade of melatoninergic activity with specific antagonists or morpholinos would be necessary to unmask 5-HT$_{2C}$ antagonist properties. Ellis LD et al., Brain res. 1449:46-59, 2012 Nasevicious A & Ekker SC, Nat Gen 26:216-220, 2000

Disclosures: N. Ribeiro Palha: None. **A. Dekeyne:** None. **S. Veiga:** None. **W. Boucheron:** None. **P. Delagrange:** None. **C. Louis:** None. **P. Lestage:** None.

Poster

772. Schizophrenia: Antipsychotics

Location: Hall A

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Program#/Poster#: 772.09/F3

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: NIMH R15MH098246

Title: Blocking cortical GABAA receptors impairs sociability in rats

Authors: *T. A. PAINE, N. SWEDLOW, L. SWETSCHINSKI;
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Abstract: *Background:* Schizophrenia is a chronic, often debilitating, disorder characterized by positive, negative and cognitive symptoms. Negative symptoms, including asociality and anhedonia, are not adequately treated by currently available medications and appear to contribute to poor outcomes of people with schizophrenia. Post-mortem analyses find reduced expression of GAD_{67} (a GABA synthesis protein) and GAT_1 (a GABA reuptake transporter) in the prefrontal cortex (PFC) of individuals diagnosed with schizophrenia; changes in these proteins suggest decreased PFC GABA function in schizophrenia. The goal of the current experiment was to determine if decreasing cortical GABA function is sufficient to cause behavioral changes reminiscent of the negative symptoms of schizophrenia. *Methods:* Rats were implanted with guide cannulae aimed at the medial PFC. Over the course of 2 weeks rats were tested on a battery of tests: the social interaction test, the social preference test and the sucrose intake test. Prior to each test rats where infused with either bicuculline (0.0, 12.5, or 25.0 ng/0.5 µl/side) or L-allylglycine (0.0, 5.0, or 10.0 µg/0.5 µl/side). *Results:* Intra-cortical infusions of the $GABA_A$ receptor antagonist bicuculline (12.5 or 25 ng/0.5 µl/side), but not the GABA synthesis inhibitor L-allylglycine, decreased both the number of social interactions and the time spent engaged in social interactions. Similarly, bicuculline (25 ng/0.5 µl/side), but not L-allylglycine, infusions reduced the rats' social preference. Neither drug affected sucrose preference. *Discussion*: Blockade of $GABA_A$ receptors, but not inhibition of GABA synthesis, decreased sociability. This effect cannot be explained by a reduction in the intrinsic rewarding property of social interactions. These results are support our previous findings that blockade of $GABA_A$ receptors, but not GABA synthesis, causes schizophrenia-like cognitive symptoms (i.e., impaired attention and decision-making). Combined these data suggest that reduced activation of $GABA_A$ receptors, rather than reduced synthesis *per se*, leads to schizophrenia-like changes in behavior.

Disclosures: T.A. Paine: None. **N. Swedlow:** None. **L. Swetschinski:** None.

Poster

772. Schizophrenia: Antipsychotics

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Program#/Poster#: 772.10/F4

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: The use of preclinical assessments of anhedonia and motor function to understand dopamine D2 receptor-mediated behavioral effects

Authors: *D. B. HORTON[1], K. DLUGOLENSKI[2], N. C. STRATMAN[2], C. J. SCHMIDT[2], T. A. CHAPPIE[2];
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Abstract: Drugs exhibiting functional dopamine D2 receptor antagonism have been characterized by a multitude of behavioral effects including motor dysfunction and anhedonia in the clinic. While motor effects can easily be assessed preclinically through locomotor activity assessments, FOBs, clinical sign monitoring or catalepsy tests, anhedonia risk can be a bit more difficult to understand. The intracranial self-stimulation (ICSS) model utilizes operant responding for electrical stimulation to assess reward sensitivity or motivation to determine the potential rewarding or anhedonic effects of drugs. The purpose of the current work was to better understand the level of translation this model has to predict negative affect or anhedonia in the clinic and the relationship that these effects have to locomotor and catalepsy assessments. Literature has shown that >70% D2 receptor occupancy is needed to induce negative subjective effects and motoric dysfunction in the clinic. The current work employed *ex vivo* receptor occupancy (RO) techniques to determine doses of two classic D2 receptor antagonists, eticlopride and haloperidol, which would afford similar D2 RO levels in rats and the effect of these doses on ICSS, locomotor activity, and catalepsy assessments, was determined. To assess ICSS effects, rats with bipolar stainless steel electrodes implanted in the medial forebrain bundle were initially trained to spin a wheel for electrical stimulation. Once stable responding was achieved, the current was held constant and a discrete trial task of varying frequencies was used to determine the ICSS threshold or the frequency at which the stimulation became rewarding. Once stable ICSS thresholds were established, the effect of eticlopride and haloperidol on ICSS thresholds were assessed as a within subjects design. In a separate group of rats, horizontal and vertical locomotor activity was assessed using automated test chambers with infrared photo-beam systems and catalepsy assessments were manually scored using a bar at a height of 10 cm above the testing surface. The current results show that eticlopride and haloperiodol, at clinically relevant D2 ROs, increased ICSS thresholds, decreased locomotor activity, and induced catalepsy at higher doses. Furthermore, the assessment of the magnitude of effect at relevant D2 ROs allows for a better understanding of what effects in these preclinical models might translate to the clinical. Taken together, the current work highlights the importance of these preclinical models to understand the potential anhedonic and motoric safety concerns associated with drugs targeting the dopaminergic system.

Disclosures: **D.B. Horton:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **K. Dlugolenski:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **N.C. Stratman:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **C.J. Schmidt:** A. Employment/Salary (full or part-time):; Pfizer, Inc. **T.A. Chappie:** A. Employment/Salary (full or part-time):; Pfizer, Inc..

Poster

772. Schizophrenia: Antipsychotics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 772.11/F5

Topic: C.19. Drug Discovery and Development

Support: MH094835 to JSB

Title: Rapastinel (GLYX-13) produces rapid transcriptomic changes associated with synaptic signaling and remodeling: toward the elucidation of the mechanisms that underlie glutamatergic rapid-acting antidepressants

Authors: *M. E. SCHMIDT[1], A. L. GROSS[1], R. A. KROES[1], J. S. BURGDORF[2], J. R. MOSKAL[1,2];
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Abstract: Rapastinel, an allosteric NMDAR modulator with characteristics of a glycine-site partial agonist, and ketamine, a NMDAR antagonist, are two rapid-acting and long-lasting antidepressants. Given their similar antidepressant activity but divergent pharmacology, the transcriptomic profiles underlying the molecular mechanisms were assessed. Focused microarrays were used to examine changes in the expression of 1,178 CNS-specific genes in the rat medial prefrontal cortex at 1hr, 24hrs, and 2 weeks following treatment with a single, optimal antidepressant dose of either rapastinel (3mg/kg, IV) or ketamine (10mg/kg, IV). SAM analysis was used to quantify significant gene expression changes and was followed by functional annotation and identification of enriched biological pathways using DAVID, GSEA, and IPA. Rapastinel significantly enriched synaptic signaling pathways at 1hr post-dosing including; vesicle trafficking, ion channel activity, and a range of second messenger pathways. The effect of ketamine on these synaptic signaling pathways was not significant until 24hrs following treatment. Long-term potentiation (LTP) was enhanced by rapastinel at 24hrs and persisted up to 2 weeks, whereas ketamine only enriched LTP at 24hrs. Both rapastinel and ketamine enriched pathways related to synaptic remodeling, including cellular morphogenesis and differentiation. However, individual gene expression differences showed that rapastinel clearly induced these changes quicker, at 1hr and 24hrs, while ketamine did not affect these transcripts until 24hrs and 2 weeks. These data lend support to the hypothesis that rapastinel facilitates the enhancement of synaptic signaling through remodeling at the synapse by direct activation of the NMDA receptor, while ketamine likely produces these effects through an indirect pathway via downstream activation.

Disclosures: **M.E. Schmidt:** A. Employment/Salary (full or part-time):; Naurex, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex, Inc. **A.L. Gross:** A. Employment/Salary (full or part-time):; Naurex, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex, Inc. **R.A. Kroes:** A. Employment/Salary (full or part-time):; Naurex, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex, Inc. **J.S. Burgdorf:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex, Inc. F. Consulting Fees (e.g., advisory boards); Naurex, Inc. **J.R. Moskal:** A. Employment/Salary (full or part-time):; Naurex, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex, Inc.

Poster

772. Schizophrenia: Antipsychotics

Location: Hall A

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Program#/Poster#: 772.12/F6

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: The involvement of dopamine D_1 signaling on the cognitive function and the cataleptic effect of a phosphodiesterase 10A inhibitor, PDM-042 in rats

Authors: ***S. MAEHARA**, K. ARAKAWA, N. YUGE, S. FURUSAKO;
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Abstract: Phosphodiesterase 10A (PDE10A) is a new potential target for the treatment of schizophrenia. PDE10A, via hydrolysis of cAMP and cGMP, regulates intracellular cyclic nucleotide signaling cascades within the striatal medium spiny neurons. PDE10A inhibitors activate both the D_2 receptor-expressing indirect pathway and the D_1 receptor-expressing direct pathway in the striatal medium spiny neurons. Here we examined the pharmacological effects and the involvement of dopamine D_1 signaling of the potent, selective, orally available, and brain penetrable PDE10A inhibitor, PDM-042 in rats. PDM-042 inhibited human and rat PDE10A activities with IC_{50} values of less than 1 nM. The compound was more than 1000-fold selective against other PDEs and had no significant off-target activities against other pharmacological targets including large panels of GPCRs, enzymes, and ion channels. The radiolabeled PDE10A inhibitor, [^{3}H]PDM-042 exhibited saturation binding curves and high affinity with a K_d value of

8.5 nM for membranes prepared from rat striatum. PDM-042 itself and other structurally unrelated PDE10A inhibitors displaced [^{3}H]PDM-042 binding to PDE10A in a concentration-dependent manner. *In vivo* PDE10A occupancy rate of PDM-042 showed a good correlation with both the dose and the plasma concentration of PDM-042. In behavioral tests, PDM-042 dose-dependently (0.1 to 1 mg/kg, p.o.) attenuated the conditioned avoidance response (CAR), a well established preclinical predictor of antipsychotic activity. PDM-042 at doses of 1 and 3 mg/kg, p.o. showed better discrimination of a novel object from a familiar one 48 hours after the acquisition trial in the object recognition test, indicating its favorable effect on cognitive function. A D_1 receptor antagonist, SCH23390, significantly blocked the increase of object recognition memory caused by PDM-042 without affecting recognition index by itself. Regarding side effects, PDM-042 had a minimal effect on catalepsy even at a 30-fold higher dose (10 mg/kg, p.o.) than the efficacious dose in the CAR, while risperidone elicited catalepsy in a dose-dependent manner. SCH23390 significantly enhanced the duration of catalepsy caused by PDM-042 (1 mg/kg, p.o.) in a dose-dependent manner (0.003 to 0.03 mg/kg, s.c.), while SCH23390 alone slightly increased the duration of catalepsy up to 0.1 mg/kg, s.c.The present results suggest that PDE10A inhibitor may be the novel treatment of schizophrenia with antipsychotic actions, cognitive enhancing effects, and few extrapyramidal side effects, and that the enhancement of D_1 signaling involves in the cognitive enhancing effect and the cataleptic effect of PDE10A inhibitor in rats.

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Poster

772. Schizophrenia: Antipsychotics

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Program#/Poster#: 772.13/F7

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: The atypical antipsychotic amisulpride shares discriminative stimulus properties with benzamide derivatives, but not with antipsychotic, antidepressant, or anxiolytic drugs from other chemical classes

Authors: *T. J. DONAHUE[1], K. A. WEBSTER[1], T. M. HILLHOUSE[3], C. H. COOPER[1], K. W. LOVELESS[1], E. M. LEVIT[1], A. R. GRANT[1], R. YOUNG[2], E. O. DE OLIVEIRA[4], J. H. PORTER[1];
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VA; [3]Dept. of Pharmacol., Univ. of Michigan, Ann Arbor, MI; [4]Ctr. for Drug Discovery, Georgetown Univ., Washington, DC

Abstract: Amisulpride, a benzamine derivative, is a second generation (atypical) antipsychotic drug used to treat both schizophrenia (at high doses) and depression (at low doses). The relatively selective binding profile of amisulpride distinguishes it from most other antipsychotic drugs, by primarily targeting dopamine D2 and D3 receptors and serotonin 5-HT2B and 5-HT7 receptors, where it displays functional antagonist activity. Approved in Europe, amisulpride displays an atypical clinical profile with efficacy for both positive and negative symptoms and with reduced extrapyramidal motor effects. The present study compared the discriminative stimulus properties of amisulpride to other benzamide derivatives and to antipsychotic, antidepressant, and anxiolytic drugs. Adult male C57BL/6 mice (N=14) were trained to discriminate 10 mg/kg rac-amisulpride from vehicle in a two-lever drug discrimination task for food reinforcement in an average of 35.7 sessions (range 6-89). The amisulpride dose-response curve (0.078 - 20.0 mg/kg) yielded an ED50 = 0.73 mg/kg 95% (CI = 0.47-1.13 mg/kg). Substitution testing with other benzamide derivatives revealed that amisulpride fully generalized (> 80% Drug Lever Responding) to sulpiride ED50 = 7.29 mg/kg (C.I. = 3.73-14.28 mg/kg) and partially to raclopride at 0.10 mg/kg (62.7% DLR) and tiapride at 40.0 mg/kg (76.4% DLR), but not to nemonapride or zacopride. In contrast, the antipsychotic drugs haloperidol, chlorpromazine, clozapine, olanzapine, risperidone, quetiapine, and aripiprazole; the antidepressant drugs fluoxetine, mianserin, imipramine, and bupropion; and the anxiolytic drug chlordiazepoxide did not produce amisulpride-appropriate responding during substitution testing. These findings demonstrate that the atypical antipsychotic amisulpride shares discriminative stimulus properties with some, but not all, benzamide derivatives such as the antipsychotic sulpiride that are structurally similar; however, amisulpride does not share discriminative stimulus properties with antipsychotic, antidepressant and anxiolytic drugs that belong to other drug classes. These results demonstrate that amisulpride possesses a unique discriminative stimulus.

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Poster

772. Schizophrenia: Antipsychotics

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Support: Migraine Research Foundation

Naurex Inc.

Title: Suppression of spreading depolarization and stabilization of dendritic spines by rapastinel (GLYX-13), an NMDA receptor glycine-site functional partial agonist

Authors: *X.-L. ZHANG[1], C. W. SHUTTLEWORTH[3], J. R. MOSKAL[4], P. K. STANTON[2]; [2]Cell Biol. & Anat., [1]New York Med. Coll, Valhalla, NY; [3]Dept. of Neurosciences, Univ. of New Mexico Sch. of Med., Albuquerque, NM; [4]Dept. of Biomed. Engin., Northwestern Univ., Evanston, IL

Abstract: Cortical spreading depolarization (SD) is a slow self-propagating wave of mass cellular depolarization in brain tissue, thought to be the underlying cause of migraine scintillating scotoma and aura, and associated with stroke, traumatic brain injury, and termination of status epilepticus. The N-methyl-D-aspartate subtype of glutamate receptor (NMDAR), which gates influx of calcium and is an important trigger of long-term synaptic plasticity, is also a contributor to the initiation and propagation of SD. The current study tested the potential of pharmacological modulation of NMDAR activity through the obligatory co-agonist binding site, to modulate the propagation of SD triggered by a focal elevation in extracellular [K+] in stratum radiatum of field CA1, and modulate the effects of SD on dendritic spine morphology, in hippocampal slices *in vitro*. A novel NMDAR functional glycine site partial agonist, rapastinel (aka GLYX-13), sometimes prevented the induction of SD, and when it occurred, significantly slowed its rate of propagation. In a subset of slices, a primary SD triggered by a focal puff of high [K+] resulted in a delayed, secondary SD initiated at the border between pyramidal cell bodies and stratum oriens. Rapastinel always blocked the induction of these secondary SDs. The passage of SD through CA1 stratum radiatum produced a rapid retraction of apical dendritic spines which reversed to an overshooting increase in spine volume after neuronal depolarization had recovered. Rapastinel improved the rate and extent of return of dendritic spines to their original sizes and locations following SD, suggesting that NMDAR modulators can protect synaptic connections in the brain from structural alterations elicited by SD. These data indicate that NMDAR modulation to renormalize activity may be an effective new treatment strategy for suppression or amelioration of the contribution of SD to short and long-term symptoms of migraine attacks, as well as SD following stroke and traumatic brain injury.

Disclosures: X. Zhang: None. **C.W. Shuttleworth:** None. **J.R. Moskal:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Founder of Naurex Inc., has founder's shares of stock and receives financial compensation as a consultant. **P.K. Stanton:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual

funds); Receives stock in Naurex Inc.. F. Consulting Fees (e.g., advisory boards); Receives financial compensation as a consultant to Naurex Inc..

Poster

772. Schizophrenia: Antipsychotics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 772.15/F9

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: Natural Sciences and Engineering Research Council of Canada

Title: Changes in brain volume in response to estradiol levels, amphetamine sensitization and haloperidol treatment in awake female rats

Authors: D. MADULARU[1], *P. P. KULKARNI[2], C. F. FERRIS[2], W. G. BRAKE[1]; [1]Psychology, Concordia Univ., Montreal, QC, Canada; [2]Psychology, Northeastern Univ., Boston, MA

Abstract: Estrogen has been shown to further ameliorate symptoms when administered in conjunction with antipsychotics in patients with schizophrenia. We have previously shown that chronic haloperidol (HAL) treatment reduces amphetamine (AMPH)-induced locomotor activity in AMPH-sensitized rats, but only when paired with high levels of the estrogen, 17-β estradiol. In addition, we reported estradiol-dependent responses to AMPH in AMPH-sensitized rats as measured by functional magnetic resonance imaging. It is thus clear that estradiol and antipsychotics both affect the rat brain, however the mechanism by which this occurs is unknown. The aim of the current study was to assess this interaction by investigating the effects of estradiol, AMPH and HAL on brain volume changes in awake female rats. Repeated exposure to AMPH resulted in an overall reduction in brain volume, regardless of hormonal status (i.e. no, low or high estradiol). Similarly, chronic HAL treatment further reduced brain volume compared to acute treatment. Hormonal status affected hippocampal volume with rats receiving low estradiol replacement showing larger volume; this difference was no longer significant after repeated exposure to AMPH. Finally, we found changes in volume in response to AMPH throughout hippocampal components (i.e. CA1, CA2, CA3 and dentate) as well as components of the mesocortical system. In conclusion, brain morphology seems to be influenced by hormonal status, as well as exposure to AMPH and haloperidol treatment. These findings implicate areas where estradiol, amphetamine and antipsychotics may be producing volumetric changes in the brain, pointing the way to where future studies should focus.

Disclosures: **D. Madularu:** None. **P.P. Kulkarni:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ekam Solutions LLC. **C.F. Ferris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ekam Solutions LLC. **W.G. Brake:** None.

Poster

772. Schizophrenia: Antipsychotics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 772.16/F10

Topic: C.19. Drug Discovery and Development

Support: Naurex research grant

Title: GLYX-13 ameliorates acute ketamine and sub-chronic ketamine- and phencyclidine-induced memory deficits in C57BL/6J mice

Authors: ***H. Y. MELTZER**[1], L. RAJAGOPAL[1], J. S. BURGDORF[2,4], J. R. MOSKAL[3,4]; [1]Northwestern Univ. Sch. of Med., Chicago, IL; [2]Falk Ctr. for Mol. Therapeut., [3]Biomed. Engineering, McCormick Sch. of Engin., Northwestern Univ., Evanston, IL; [4]Naurex Inc., Evanston, IL

Abstract: Background: Rapastinel (GLYX-13) is a tetrapeptide (Thr-Pro-Pro-Thr-amide) which acts as an N-methyl-D-aspartate receptor (NMDAR) glycine site functional partial agonist. It is currently in development, as is the NMDAR noncompetitive antagonist, ketamine, as a rapidly acting antidepressant. Acute or sub-chronic (sc) administration to rodents of the NMDAR antagonists, ketamine and phencyclidine (PCP), produces transient or enduring, respectively, deficits in novel object recognition (NOR), an analog of human declarative memory. We predicted that rapastinel would not impair NOR and might be able to ameliorate the cognitive deficit produced by ketamine or PCP in rodents. Methods: Four cohorts of male C57BL/6J mice (N=10-12 per group) were used for these studies. The method for studying NOR has been reported (Horiguchi et al., 2012, Psychophamacology (Berl). 221(2): 205-15). In the acute study, mice were given saline (sal, i.v.), ketamine (30 mg/kg, i.p.) or rapastinel (1 mg/kg; i.v.)+acute ketamine (30 mg/kg; i.p.) 30 min prior to NOR testing. For the sc studies, groups of mice were given sal, PCP (10 mg/kg; b.i.d. or ketamine (30 mg/kg; b.i.d) for 7 days, followed by 7 days washout). The scPCP and scketamine mice were given rapastinel (0.3 or 1 mg/kg; i.v.) 30 min prior to NOR testing. The scsal group received saline. Results: Ketamine impaired NOR as indicated by a discrimination index of -0,008, due to equivalent exploration of novel and familiar

objects. Prior treatment with rapastinel (1 mg/kg) significantly prevented the ketamine-induced NOR deficit (**P<0.01). Rapastinel (1 mg/kg, i.v. ***P<0.001), but not 0.3 mg/kg (P>.05), significantly reversed both the scPCP- and scketamine-induced NOR deficit. NOR was normal in the sal-treated mice. Conclusion: These findings suggest that rapastinel differs from ketamine in not producing an acute disruption of NOR and can prevent the NOR impairment produced by acute ketamine. Its ability to restore NOR after scPCP or scketamine is consistent with its learning and memory enhancement in a variety of hippocampal-dependent learning tasks, in both young adult and learning-impaired aged rats. Similar effects have been reported with atypical antipsychotic drugs which are effective in improving cognitive impairment in schizophrenia, whereas acute ketamine has been reported to produce cognitive impairment and psychopathology in some normal volunteers and patients with schizophrenia. Testing of rapastinel to treat cognitive impairment in schizophrenia and major depression is indicated.

Disclosures: **H.Y. Meltzer:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research grant. F. Consulting Fees (e.g., advisory boards); Consultant. **L. Rajagopal:** None. **J.S. Burgdorf:** A. Employment/Salary (full or part-time):; Employee. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stockowner. **J.R. Moskal:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex employee and stock owner.

Poster

772. Schizophrenia: Antipsychotics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 772.17/F11

Topic: C.19. Drug Discovery and Development

Support: MH094835 to JSB

Title: The effects of rapastinel (GLYX-13), a NMDA receptor allosteric modulator, on the mTOR signaling pathway transcriptome

Authors: ***A. L. GROSS**[1], M. E. SCHMIDT[1], R. A. KROES[1], J. S. BURGDORF[2], J. R. MOSKAL[1,2];
[1]Naurex Inc, Evanston, IL; [2]Biomed. Engineering, McCormick Sch. of Engineering, Northwestern Univ., Falk Ctr. for Mol. Therapeut., Evanston, IL

Abstract: Activation of the mTOR signaling pathway in the rat medial prefrontal cortex (MPFC) is known to be part of the molecular mechanism underlying the rapid-acting antidepressant effect of ketamine, a NMDA receptor (NMDAR) antagonist. Rapastinel has characteristics of a glycine-site partial agonist. It also produces rapid, and long-lasting antidepressant effects, but without the side-effects seen with ketamine. A comparison of mTOR signaling pathway gene expression patterns between rapastinel and ketamine was undertaken using a Qiagen mTOR pathway-specific qRT-PCR array. Rats were given a single, optimal antidepressant dose of either rapastinel (3 mg/kg, IV) or ketamine (10 mg/kg, IV), and gene expression was measured in the MPFC at 1 hour, 24 hours, and 2 weeks post-dosing. At 1 hr post-administration, rapastinel led to the upregulation of 8 genes (Akt3, Mapk1, Pik3r1, Prkab2, Prkca, Stk11, Tsc1, Gsk3b), as compared to ketamine, which upregulated 16 genes (Akt3, Mapk1, Pik3r1, Prkab2, Prkca, Stk11, Tsc1, Insr, Kras, Mlst8, Nras, Prkaa2, Pten, Prs6ka2, Ddit4, Sgk1). Rapastinel, unlike ketamine, downregulated Prkag1, which leads to enhanced mTOR complex formation. After 24 hr, there were minimal gene expression changes detected by either rapastinel or ketamine. Expression of only one gene was affected by rapastinel (Redd2, a negative regulator of both mTORC1 and mTORC2 was downregulated) and 4 genes were affected by ketamine (Redd1, and Sgk1 were both upregulated, and Ppp2r4 and Ilk, modulators of the mTOR complex formation, were both downregulated). After 2 wks, no transcriptomic changes were observed following rapastinel. However, the differential expression of Redd1 and ppp2r4 persisted, and Hspa4 was also upregulated following ketamine. Treatment with rapastinel and ketamine both markedly impacted the mTOR signaling pathway transcriptome within 1 hr. However, ketamine modulated significantly more genes in this transcriptome than rapastinel and the effects of ketamine persisted for up to 2 wks post dosing.

Disclosures: **A.L. Gross:** A. Employment/Salary (full or part-time):; Naurex, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex, Inc. **M.E. Schmidt:** A. Employment/Salary (full or part-time):; Naurex, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex, Inc. **R.A. Kroes:** A. Employment/Salary (full or part-time):; Naurex, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex, Inc. **J.S. Burgdorf:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex, Inc.. F. Consulting Fees (e.g., advisory boards); Naurex, Inc. **J.R. Moskal:** A. Employment/Salary (full or part-time):; Naurex, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex, Inc..

Poster

772. Schizophrenia: Antipsychotics

Location: Hall A

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Topic: C.19. Drug Discovery and Development

Support: Swedish Society for Medical Research

Åhlenstiftelsen

Magnus Bergvalls stiftelse

Stiftelsen Lars Hiertas Minne

Karolinska Institutet funds

Swedish Research Council grant 21785-01-4

Swedish Research Council grant 15083

Title: The fast-off hypothesis revisited: A functional kinetic study of antipsychotic antagonism of the dopamine D2 receptor

Authors: *J. NILSSON[1], K. SAHLHOLM[2], H. ZEBERG[2], S. ÖGREN[2], P. ÅRHEM[2];
[1]Dept. of Neurosci., [2]Karolinska Institutet, Stockholm, Sweden

Abstract: Rapid dissociation from the dopamine D2 receptor (D2R) has been proposed to confer antipsychotic atypicality. Furthermore, antipsychotic D2R affinities have been proposed to reflect differences in dissociation rate constants (koff), while association rate constants (kon) were claimed to be similar (Seeman and Kapur, 2000). However, kon was not directly measured in previous studies. Since affinity is determined by the ratio koff /kon, low-affinity D2R antagonists would be atypical antipsychotics, and vice versa. This so-called "fast-off" hypothesis has recently inspired the development of new fast dissociating D2R antagonists. We recently reported on the relative rates of response recovery from D2R antagonism using electrophysiology to measure D2R-induced opening of G protein-coupled inward rectifier K+ channels (GIRK). Whereas no response recovery was observed with haloperidol (typical antipsychotic), differences in rates of recovery upon washout of chlorpromazine (typical) and clozapine (atypical) were surprisingly small. Furthermore, lipophilic compounds displayed a component of antagonism which could not be washed out. Recent studies suggest that lipophilic membrane accumulation can cause underestimation of ligand koff. We thus tested whether increasing the dopamine (DA) concentration 100-fold to outcompete lipophilic antagonists from the D2R binding site would affect recovery from antipsychotic inhibition. We also reexamined the variability of antipsychotic kon, capitalizing on the GIRK assay's temporal resolution. We

estimated kon from the experimental recordings, using an expression derived from a kinetic scheme assumed to describe the binding process. Our new data indicate that the kons of antipsychotics vary more widely than previously claimed, whereas koffs are more similar across compounds. Moreover, lipophilicity-driven accumulation might interfere with koff estimation, as increasing the dopamine concentration revealed a surprisingly fast recovery from inhibition by haloperidol, which in our previous study exhibited long-lasting D2R antagonism. Finally, affinities calculated using our kon and koff estimates correlate well with functional potency (IC50) determined using our GIRK assay, and with affinities reported from radioligand binding studies.

Disclosures: J. Nilsson: None. **K. Sahlholm:** None. **H. Zeberg:** None. **S. Ögren:** None. **P. Århem:** None.

Poster

772. Schizophrenia: Antipsychotics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: C.19. Drug Discovery and Development

Support: NIH Grant MH094835

Title: Insulin-like growth factor i produces an antidepressant-like effect through modulation of n-methyl-d-aspartate receptor-independent long-term potentiation-like synaptic plasticity

Authors: *E. M. COLECHIO[1], J. BURGDORF[2], X.-L. ZHANG[4], A. GROSS[5], R. A. KROES[5], P. K. STANTON[4], J. R. MOSKAL[5,3];
[1]Dept Neurosci, [2]Falk Ctr. for Mol. Therapeut., [3]Northwestern Univ., Evanston, IL; [4]Cell Biol. and Anat., New York Med. Col., Valhalla, NY; [5]Naurex, Inc., Evanston, IL

Abstract: Growth factors play an important role in regulating neurogenesis, synapse formation, and may be involved in modulating the antidepressant response to conventional antidepressants. To date, insulin-like growth factor I (IGFI) is the only growth factor that has shown antidepressant properties in human clinical trials. However, its mechanism of action remains unclear. A single dose of IGFI IV (0.1 mg/kg) or intra-medial prefrontal cortex (MPFC; 0.1-1 μg) activated IGFI receptors (IGFIRs) in the MPFC and reversed the depressive-like phenotype of chronic unpredictable stress using the Porsolt, sucrose preference, novelty induced hypophagia, and ultrasonic vocalization models at 1 hr to 2 weeks post-dosing in rats. These effects were blocked by pretreatment with either the IGFIR antagonist JB1 or the protein

synthesis inhibitor anisomycin. When the AMPA/kainate antagonist NBQX was administered 24 hrs post-IGFI injection, the long-lasting antidepressant-like effects of IGFI were blocked. Application of IGFI (200 nM) to rat hippocampal slices *in vitro* increased synaptic strength both in Schaffer collateral CA1 synapses and in medial prefrontal cortex layer V synapses. IGFI-induced potentiation of synaptic strength was blocked by JB1 and anisomycin, but not the NMDAR antagonist D-AP5. When rats were treated with IGFI (0.1 mg/kg IV), and hippocampal slices were prepared 24 hrs later, stimulus-evoked long-term potentiation (LTP) at Schaffer collateral-CA1 synapses was larger than that observed in saline controls. These data support the conclusion that the antidepressant-like effects of IGFI are mediated by a NMDA receptor independent LTP-like synaptic plasticity mechanism requiring both IGFIR activation and ongoing protein synthesis.

Disclosures: E.M. Colechio: None. **J. Burgdorf:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex, Inc.. F. Consulting Fees (e.g., advisory boards); Naurex, Inc. **X. Zhang:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Naurex, Inc. **A. Gross:** A. Employment/Salary (full or part-time):; Naurex, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex, Inc. **R.A. Kroes:** A. Employment/Salary (full or part-time):; Naurex, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex, Inc. **P.K. Stanton:** F. Consulting Fees (e.g., advisory boards); Naurex, Inc. **J.R. Moskal:** A. Employment/Salary (full or part-time):; Naurex, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex, Inc..

Poster

772. Schizophrenia: Antipsychotics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: C.19. Drug Discovery and Development

Support: MH094835 to JSB

Title: Rapastinel (GLYX-13), an N-methyl-D-aspartate functional glycine site partial agonist, is efficacious in rat surgical models of neuropathic pain

Authors: *N. GHOREISHI-HAACK[1], J. BURGDOF[2], R. M. BURCH[3], J. R. MOSKAL[3,2]; [1]Naurex Inc, Skokie, IL; [2]Northwestern Univ., Evanston, IL; [3]Naurex Inc., Evanston, IL

Abstract: Rapastinel is an amidated tetrapeptide (Thr-Pro-Pro-Thr-amide) currently in Phase II clinical trials for major depressive disorder, and is also being developed as a therapeutic for neuropathic pain. Previously, it was shown that rapastinel (5 mg/kg IV) produces an analgesic effect in the late phase of the rat formalin model of neuropathic pain. Medial prefrontal cortex (prelimbic or infralimbic) injection of rapastinel (0.1, 1, or 10 μg/side) produced an analgesic effect in the late phase of the rat formalin model (compared to saline vehicle) for up to 1 month following a single dose as measured by weighted pain score. Rapastinel was also evaluated in two rat surgical models of the neuropathic pain: the Chung (spinal nerve ligation) and the Bennett (chronic sciatic nerve constriction) models. Pain responses were measured using Von Frey filaments and Dixon up-down method. At ED100 (5mg/kg, IV), rapastinel produced a robust analgesic effect (as compared to saline vehicle) in these models at 1 hr, 24 hrs and 1 week following a single dose, without any adverse effects. In comparison, the analgesic effect of a single dose of gabapentin (150 mg/kg PO) was observed at 1 hr but not 24 hrs or 1 week. In addition, rapastinel was evaluated in two rat models of nociceptive pain: the carrageenan inflammatory model and the tail flick model. Pain responses in response to carrageenan (administered in the plantar surface of the right hind paw) were measured using Von Frey filaments and the Dixon up-down method. Pain responses for the tail flick model were measured by tail withdrawal latency in response to a radiant heat stimulus. Rapastinel did not produce any effect when evaluated in either of these models. Rapastinel did not produce sedation or psychotomimetic-predictive effects in the rotarod or the open field test across a wide dose range (therapeutic index of > 100). These data show that rapastinel has therapeutic potential for the treatment of neuropathic pain

Disclosures: **N. Ghoreishi-Haack:** A. Employment/Salary (full or part-time):; Naurex Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex Inc. **J. Burgdof:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex Inc.. F. Consulting Fees (e.g., advisory boards); Naurex Inc. **R.M. Burch:** A. Employment/Salary (full or part-time):; Naurex Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex Inc. **J.R. Moskal:** A. Employment/Salary (full or part-time):; Naurex Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex Inc..

Poster

772. Schizophrenia: Antipsychotics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 772.21/F15

Topic: C.19. Drug Discovery and Development

Title: Rapastinel (GLYX-13), an allosteric NMDA receptor modulator, exerts its antidepressant effects by acting at a novel NMDA receptor binding site

Authors: *R. A. KROES[1], J. S. BURGDORF[2], A. L. GROSS[1], M. A. KHAN[1], X. ZHANG[3], R. M. BURCH[1], P. K. STANTON[3], J. R. MOSKAL[1,2];
[1]Naurex, Inc., Evanston, IL; [2]Northwestern Univ., Evanston, IL; [3]New York Med. Col., Valhalla, NY

Abstract: Rapastinel, a NMDAR modulator that has characteristics of a glycine site partial agonist, is currently in Phase II clinical development for treatment-resistant depression. The present studies detail the *in vitro* characteristics of rapastinel. Functional glycine site agonist effects were measured using [3H]MK-801 potentiation assays in membrane extracts prepared from rat cortex and human NR2 subtype-expressing HEK cells. In cortical extracts, rapastinel exhibits partial agonist activity (EC50 64nM; 26.1% activity relative to glycine). In recombinant human NR2-expressing HEK cells, partial agonist activity of rapastinel was also demonstrated at all 4 receptor subtypes (EC50 of 14pM, 2.4nM, 19.9nm, and 7.8pm and activities of 39.5%, 39.0%, 56.8%, and 59.2%, at NR2A, NR2B, NR2C, and NR2D, respectively). Functional antagonist effects were determined using pA2 response shift analysis of NMDAR current from CA1 pyramidal neurons in rat hippocampal slices. Rapastinel also demonstrated antagonist-like activity (Kp 1.3μM) in hippocampal slices in the presence of glycine. Direct interaction of rapastinel at the glycine site of the NMDAR was assessed by (i) radioligand displacement of [3H]glycine and [3H]L-689,560, (ii) [3H]MK-801 binding in the presence of 5,7 dichlorokyneurenic acid (DCK), and (iii) [3H]MK-801 binding in recombinant hNR2-expressing HEK cells containing a mutant, non-functional glycine site. Radioligand competition studies showed that rapastinel had no effect on [3H]glycine binding in cortical membranes, and while glycine and D-cycloserine competed with the high affinity glycine site antagonist [3H]L-689,560, rapastinel did not. Rapastinel remained fully active in the presence of 5,7DCK. Point mutations within the glycine site, while totally inhibiting glycine activity, had no effect on the ability of rapastinel to modulate channel opening in any of the NMDAR subtypes. Rapastinel did not influence the ability of glutamate, spermidine, or ifenprodil to modulate NMDAR channel opening. Molecular modeling in silico identified a potential high affinity rapastinel binding site within the amino terminal domain of NR2B. Point mutagenesis of critical amino acids within this binding site, while leaving glycine activity unaffected, significantly inhibited rapastinel activity in [3H]MK-801 assays using recombinant human NMDAR2B-expressing HEK cells. These data suggest that rapastinel is an allosteric NMDAR modulator with glycine-site partial agonist properties attributable to binding to a novel site on the NMDAR.

Disclosures: **R.A. Kroes:** A. Employment/Salary (full or part-time):; Naurex, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex, Inc. **J.S. Burgdorf:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex, Inc.. F. Consulting Fees (e.g., advisory boards); Naurex, Inc. **A.L. Gross:** A. Employment/Salary (full or part-time):; Naurex, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex, Inc. **M.A. Khan:** A. Employment/Salary (full or part-time):; Naurex, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex, Inc. **X. Zhang:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Naurex, Inc. **R.M. Burch:** A. Employment/Salary (full or part-time):; Naurex, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex, Inc. **P.K. Stanton:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Naurex, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex, Inc.. F. Consulting Fees (e.g., advisory boards); Naurex, Inc. **J.R. Moskal:** A. Employment/Salary (full or part-time):; Naurex, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex, Inc..

Poster

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Support: MH094835 to JSB

NS044421 to PKS

Title: NRX-1074, an NMDA receptor modulator with glycine site partial agonist properties, induces rapid and long-lasting antidepressant-like effects in rats

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Abstract: Rapastinel (GLYX-13) is an allosteric NMDA receptor (NMDAR) modulator with characteristics of a glycine-site partial agonist that shows rapid and long-lasting antidepressant activity in rodent models and humans with a favorable side-effect profile. NRX-1074 is an orally bioavailable analog of rapastinel (Thr-Pro-Pro-Thr-amide) that is benzylated at the second proline. The present studies describe the *in vitro* and *in vivo* pharmacology of NRX-1074. NMDAR activation was assessed by measuring [3H]MK-801 binding to rat cortical membranes in the presence of glutamate but in the absence of glycine. Antidepressant-like effects were determined using the rat Porsolt test at 1hr, 24 hrs and 1 week post-dosing. Learning and memory effects were measured using the positive emotional learning (PEL) test. Long-term potentiation (LTP) was measured at Schaffer collateral CA1 synapses in rat hippocampal slices prepared 24 hrs to 4 wks post-dosing. Sedative and/or ataxic effects were measured in the rat Rota-Rod test at 0.5 to 24 hrs post-dosing. Oral bioavailability was measured in rat plasma by LC/MS/MS. NRX-1074 is more potent than rapastinel in activating the NMDAR (EC50 0.2 pM vs. 64 nM), producing an antidepressant-like effect in the Porsolt test (ED50 5 ng/kg IV vs. 1 mg/kg IV), and facilitating hippocampal LTP (equivalent enhancement at 0.01 mg/kg IV vs. 3 mg/kg IV). NRX-1074 (1 mg/kg PO) also enhanced learning and memory in the PEL test. Unlike rapastinel, NRX-1074 is orally bioavailable and does not exhibit a U-shaped dose response curve in the Porsolt and LTP assays. Similar to rapastinel, NRX-1074 does not show sedative and/or ataxic effects in the Rota-Rod test (NOEL > 100 mg/kg PO). These data demonstrate that NRX-1074 is an orally bioavailable analog of rapastinel that shows increased potency, a wider therapeutic dose range, and does not show the side effects typically found with NMDAR antagonists.

Disclosures: J.S. Burgdorf: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex Inc.. F. Consulting Fees (e.g., advisory boards); Naurex Inc. **R.A. Kroes:** A. Employment/Salary (full or part-time):; Naurex Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex Inc. **X.L. Zhang:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Naurex Inc. **A.L. Gross:** A. Employment/Salary (full or part-time):; Naurex Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex Inc. **R.M. Burch:** A. Employment/Salary (full or part-time):; Naurex Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex Inc. **P.K. Stanton:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Naurex Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder,

excluding diversified mutual funds); Naurex Inc.. F. Consulting Fees (e.g., advisory boards); Naurex Inc. **M.A. Khan:** A. Employment/Salary (full or part-time):; Naurex Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex Inc. **J.R. Moskal:** A. Employment/Salary (full or part-time):; Naurex Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Naurex Inc..

Poster

772. Schizophrenia: Antipsychotics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 772.23/F17

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: The role of glucocorticoid receptors in the development of behavioural sensitisation to MK-801

Authors: *E. LEFEVRE[1], S. ALEXANDER[1,2], D. W. EYLES[1,2], T. H. J. BURNE[1,2]; [1]Queensland Brain Inst., Brisbane, Australia; [2]Queensland Ctr. for Mental Hlth. Res., Wacol, Australia

Abstract: Behavioural sensitisation can occur as a result of repeated and intermittent psychostimulant exposure and is used in rodents to model addiction and schizophrenia pathophysiology. There is evidence to suggest that sensitisation can be modulated by stress-induced factors including corticosterone (CORT) signalling via glucocorticoid receptors (GR's). The N-methyl-D-aspartate receptor (NMDAR) antagonist MK-801 is commonly used to induce NMDAR hypofunction in animals as a pharmacological model of schizophrenia. Few preclinical studies have examined the effects of stress on MK-801 sensitisation. Therefore, the present study sought to determine whether GR antagonism could inhibit the development and expression of sensitisation to the locomotor stimulatory effects of MK-801, as is reported for sensitisation to other psychostimulants. Firstly, the MK-801 sensitisation paradigm was established by modulating factors including MK-801 dose, context and rat strain. Overall, we found that Sprague Dawley (vs. Wistar) rats developed a robust sensitisation to an intermediate dose (0.25mg/kg compared to 0.1 and 0.5mg/kg) of MK-801 and this sensitisation was unaffected by the context in which MK-801 administrations were paired (home vs. novel). Based on these foundations, the effect of concomitant treatment with the GR antagonist mifepristone (RU486, 20mg/kg) on MK-801 (0.25mg/kg) induced sensitisation was examined. Adult male Sprague Dawley rats were assigned to four treatment groups: vehicle+Saline, vehicle+MK-801,

RU486+Saline and RU486+MK-801. Injections (i.p.) were administered once daily for 7 consecutive days in the test context. After 5 days withdrawal in the home cage, the expression of sensitisation was determined by challenging all groups with MK-801 (0.25mg/kg). We show that co-administration of RU486 with MK-801 augmented the development of sensitisation over the 7 day period, as well as the locomotor response to MK-801 challenge after withdrawal. Interestingly, the RU486+Saline group also displayed an enhanced response to MK-801 challenge, indicating RU486 may have long-term effects of its own. The results suggest GR antagonism has a facilitatory rather than inhibitory effect on MK-801 sensitisation, contrary to original predictions. Thus, future studies will investigate plasma CORT levels throughout the sensitisation paradigm to determine whether RU486 and MK-801 have an additive effect on CORT signalling. In conclusion, this study suggests that stress-related neural mechanisms mediating sensitisation to MK-801 is different to that of other psychostimulants.

Disclosures: E. Lefevre: None. **S. Alexander:** None. **D.W. Eyles:** None. **T.H.J. Burne:** None.

Poster

772. Schizophrenia: Antipsychotics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 772.24/F18

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: Antagonism of serotonergic 5-HT2A receptors is a sufficient, but not necessary mechanism for clozapine's discriminative stimulus properties in mice

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Abstract: One theory about the underlying neuropharmacological mechanisms responsible for the "atypicallity" of antipsychotic drugs like clozapine is the ratio of binding affinity to serotonergic 5-HT2A receptors relative to dopaminergic D2 receptors (Meltzer et al 1989). Previous studies in our lab have shown that antagonism of 5-HT2A receptors in mice is sufficient to engender clozapine-appropriate responding (Philibin et al 2009) and other studies have shown that 5-HT2A antagonism is important for some of clozapine's behavior effects such as locomotor suppression (McOmish et al 2012). The present study determined whether or not antagonism of 5-HT2A receptors is a necessary mechanism for clozapine's discriminative stimulus cue in mice by determining if 5-HT2A knockout (KO) mice could acquire clozapine's discriminative stimulus. Twelve male 5-HT2A KO mice and twelve male wild type (WT) B6129

mice were trained to discriminate 1.25 mg/kg clozapine from vehicle in a standard 2 lever drug discrimination assay for food reward. Both 5-HT2A KO and WT mice acquired the clozapine discriminative cue with WT mice (mean = 25.2 days, SEM = 3.3) acquiring the cue faster than KO mice (mean = 34.7 days, SEM = 3.8). Clozapine generalization testing revealed ED50 values of 0.61 mg/kg and 0.68 mg/kg for the 5-HT2A KO and WT mice, respectively. The atypical antipsychotic olanzapine produced full substitution for clozapine's cue in both the 5-HT2A KO mice (ED50 = 0.47 mg/kg) and WT mice (ED50 = 0.18 mg/kg). The typical antipsychotic haloperidol did not substitute for clozapine in either the 5-HT2A KO mice (42 % Drug Lever Responding at 0.4 mg/kg) or the WT mice (42% DLR at 0.4 mg/kg). Interestingly, the 5-HT2A KO mice appeared to be less sensitive to the rate suppressing effects of the atypical antipsychotics clozapine and olanzapine, but not to the typical antipsychotic haloperidol. These results are in agreement with findings by McOmish et al (2012) that 5-HT2A antagonism is important for clozapine's behavior locomotor suppression effects in mice. Finally, these results demonstrate that antagonism of serotonergic 5-HT2A receptors is not necessary (although sufficient) for mice to acquire clozapine's discriminative stimulus. We are currently exploring the mechanisms underlying clozapine's discriminative cue in 5-HT2A KO mice.

Disclosures: A. Jones: None. **K.A. Webster:** None. **C.E. McOmish:** None. **J.H. Porter:** None.

Poster

773. Mood Disorders: Antidepressants I

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 773.01/F19

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: NIH Grant DA027683

Title: Repeated paroxetine differentially modulates acoustic startle in adolescent male and female rats

Authors: *E. M. ALDERSON, Z. R. HARMONY, V. REAL, C. A. CRAWFORD;
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Abstract: Major depression is a common problem in adolescents. Unfortunately, many of the medications that are effective at relieving the symptoms of depression in adults are ineffective in adolescent populations. In addition, the most popular class of antidepressants, the selective serotonin reuptake inhibitors (SSRIs), can induce suicidal ideation in adolescents. The

mechanisms responsible for this paradoxical increase in suicidal ideation are unknown, but recent research in our laboratory suggests that paroxetine may increase anxiety in adolescent rats. In an attempt to extend these findings, we assessed the effects of repeated paroxetine treatment on the acoustic startle response (ASR), which is a measure of anxiety. Male and female Sprague-Dawley rats (N=262) were injected with paroxetine (1.25, 2.5, 5 or 10 mg/kg, IP) or vehicle for 10 consecutive days starting on postnatal day (PD) 35. Rats were then tested for ASR across 5 days starting 1, 7, or 28 days after the last drug treatment. On the first test day, rats were given 31 acoustic startle trials followed by 24 pre-pulse inhibition (PPI) trials. On the next four days, rats were given 31 acoustic startle trials to test for habituation of the ASR. Repeated paroxetine administration had a sex-dependent effect on the body weights of adolescent rats. Male rats treated with 10 mg/kg paroxetine showed a decrease in weight gain, while females given 1.25 mg/kg paroxetine exhibited a slight increase in body weight. Male rats were more sensitive to ASR than female rats, because the magnitude of the ASR was greater for males on all test days. At each age tested, exposure to paroxetine (10 mg/kg) increased habituation of the ASR (i.e., the magnitude of the ASR decreased from the first to the fifth test day) but only in male rats. Interestingly, there was a marginal interaction between sex and test day when the PPI scores were analyzed. Specifically, male rats showed increased PPI relative to females, with the greatest sex difference occurring 28 days after the last drug treatment. Overall, these data show that adolescent female rats exhibit less anxiety-like behavior than males after repeated paroxetine treatment, and these paroxetine-induced effects are still apparent four weeks after the last drug treatment.

Disclosures: E.M. Alderson: None. **Z.R. Harmony:** None. **V. Real:** None. **C.A. Crawford:** None.

Poster

773. Mood Disorders: Antidepressants I

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: NSC Grant 2013/08/M/NZ7/00518

Title: Modulation of ERK1/2 signaling pathway is the mechanism involved in antidepressant-like activity of zinc

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Abstract: Depression is one of the most debilitating medical problems concerning modern society. Over the years, a few pharmacological strategies for treating depression have been developed. Unfortunately, these strategies mainly based on interaction with monoaminergic system, are not sufficient to achieve a satisfactory level of remission in depressed patients. Recently, the N-methyl-D-aspartate (NMDA) receptor antagonists have been taken into account as alternative, potential antidepressants. Zinc (Zn) is an example of NMDA receptor antagonists which showed antidepressant-like activity in the numerous preclinical studies. It is hypothesized that antidepressant-like effects of Zn are very complex, engaging many neurotransmitters systems. Recent data indicated that serotonin and especially 5-HT1A serotonin receptors may be involved in antidepressant-like activity of Zn. Because, activation of serotonin 5-HT1A receptors are associated with activation of extracellular signal-regulated kinases 1/2 (ERK1/2) transduction signaling pathway, we tried to evaluate the involvement of ERK1/2 pathway in the antidepressant like activity of Zn using behavioral and biochemical approaches. In the Forced Swim Test (FST) performed in rats we found that the anti-immobility effect of Zn (2.5 and 5mg/kg) is prevented by MEK1/2 inhibitor U0126 (5μg/site). Moreover, we observed that active in FST Zn doses (2.5, 5 and 11.5 mg/kg) reduced the ERK1/2 phosphorylation level both in prefrontal cortex (PFC) and hippocampus (Hp) in rats, measured with Enzyme Linked-Immuno-Sorbent Assay (ELISA) method. The Zn induced reduction of ERK1/2 phosphorylation levels was observed after 15, 30 and 60 minutes in PFC, however in the Hp the effect of Zn was short lasting and was only observed after 15 and 30 minutes after Zn administration. Furthermore we showed that pretreatment with 8-OH-DPAT (5-HT1A receptor agonist; 2.5 mg/kg) prevented the Zn (5mg/kg) induced decrease in ERK1/2 phosphorylation in PFC but not in the Hp. In summary, behavioral studies indicated that antidepressant-like effect of Zn depends on the activation of ERK1/2 signaling pathways. However biochemical studies suggested that inhibition rather than activation of ERK1/2 is associated with acute Zn treatment and that Zn induced changes in ERK1/2 phosphorylation level may involve modulation of 5-HT1A signaling pathway. For an explanation of these discrepancies more detailed studies are required to describe the exact mechanisms of the Zn induced changes in ERK1/2 signaling pathways.

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Poster

773. Mood Disorders: Antidepressants I

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 773.03/F21

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: VA Grant BX11049

Title: Hdac6 inhibition induced α-tubulin acetylation translocates Gαs from lipid-rafts: a novel mechanism for antidepressant action

Authors: *H. SINGH[1,2], J. SCHAPPI[3], A. PRADHAN[4], M. RASENICK[5,2];
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Abstract: Histone deacetylase-6 (HDAC-6) enzymes involved in deacetylation of α-tubulin have been shown to be upregulated during neuropsychiatric conditions. HDAC6 knockout mice mimicked traditional antidepressant treatments. Nonetheless, a possible role for HDAC6 inhibitors in treatment of depression remains elusive. Previously we have shown that the treatment with monoamine based antidepressant drugs results in activation of G-protein subunit, Gαs, by facilitating movement out of membrane microdomains, (lipid-rafts), resulting in sustained cAMP production. Studies have also demonstrated interplay between tubulin and Gαs in lipid-rafts. Once out of lipid-raft domains, Gαs, couples with adenylyl cyclase-6 (AC-6). Although Gαs interacts directly with tubulin to modify microtubule dynamics, tubulin also acts as an anchor for Gαs in lipid rafts. Based on HDAC-6 roles in modifying α-tubulin acetylation and our data showing Gαs interactions with tubulin in lipid-raft domains, we hypothesize that acetylation of α-tubulin disrupts tubulin-Gαs anchoring, rendering Gαs free to activate AC-6 in non-raft domains. To test this, C6 glial cells were treated with HDAC-6 inhibitor, Tubastatin-A. Acetylation status of α-tubulin and localization of Gαs subunit in/out of lipid-raft membrane domains was studied. Chronic treatment with Tubastatin-A not only induced increased acetylation of a α-tubulin but also moved Gαs out of lipid-rafts, without changing total Gαs. Fluorescence Recovery After Photobleaching (FRAP) on C6 cells stably expressing Gαs-GFP, was conducted and cells pretreated with Tubastatin-A showed an "antidepressant signature". Finally, brains from mice undergoing repeated swim stress were examined and these showed decreased acetylation of α-tubulin and translocation of Gαs subunits out of lipid-rafts relative to controls. These findings suggest HDAC6 inhibition resembles chronic antidepressant treatment. Therefore, compounds that decrease tubulin-Gαs interactions by increasing acetylation of a α-tubulin may show promise for antidepressant action.

Disclosures: **H. Singh:** None. **J. Schappi:** None. **A. Pradhan:** None. **M. Rasenick:** A. Employment/Salary (full or part-time):; UIC, VA. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds

come to an institution.; Veterans Administration, NIH, Eli Lilly. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pax Neuroscience. F. Consulting Fees (e.g., advisory boards); Pfizer.

Poster

773. Mood Disorders: Antidepressants I

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 773.04/F22

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: AFSP

HDRF

Title: Sex, age and genotype differences in the responses to stress and antidepressant treatments

Authors: *C. NASCA[1], D. ZELLI[1], B. BIGIO[2], J. KOGAN[1], T. LAU[1], E. M. WATERS[1], B. S. MCEWEN[1];
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Abstract: Depression and anxiety are caused by three hits -genes, early-life experiences and stress- and are among the most common disabling medical conditions worldwide with prevalence twice as high in women than men. Excitatory amino acids, principally glutamate, are key players and normalizing their activity, through the use of external drugs, like acetyl-L-carnitine (LAC), is important for reactivation of neurochemical and morphological plasticity. Such plasticity is impaired by stress and is loss with aging. Recently, we showed that acute restraint stress (ARS) causes increased anxiety-like behavior along with a decrease in the presynaptic inhibitor of glutamate release, mGlu2 receptors, in the hippocampus of young BDNF homozygous Val male mice. Here, we investigate the effect of sex, age and genotype in the stress responses and antidepressant/anxiolytic treatments. We found that a subset of aged-matched heterozygous Met young males and females with anxiety/depressive-like behaviors show a deficit in mGlu2 expression in the hippocampal ventral dentate gyrus (vDG) along with up-regulation of the epigenetic repressor of gene transcription, REST. These molecular deficits are rapidly corrected, along with rescue of mood abnormalities, by the oral treatment with the novel antidepressant LAC using a dose that in females is twice as the one that shows efficacy in males. Young heterozygous Met males and females also differ in their response to ARS. Indeed, young heterozygous Met males show a decreased anxiety along with an elevation of mGlu2 receptors

and decrease in REST in hippocampus, whereas this positive response to stress is not observed in young heterozygous Met females, which show an exacerbation of anxiety. In regard to the age effect, we found that old heterozygous Met males show an anxiety-like behavior, which is still evident after ARS, suggesting a loss of plasticity with age in the stress response. Moreover, old heterozygous Met females show no anxiety-like behavior at baseline, but they do show anxiety after ARS, suggesting that aging exacerbates a stress response since old heterozygous Met females after stress show the same phenotype of young heterozygous Met females before applying any stress. A RNAseq specifically-targeted to the vDG is underway to reveal the clusters of genes that lead to the individual differences in response to stress and next-generation treatments. These findings suggest striking individual differences in the stress and antidepressant responses based on the sex, age and genotype and points to a window of opportunity for intervention whereby the BDNF signaling on glutamatergic function may be a target for novel epigenetic therapies.

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Poster

773. Mood Disorders: Antidepressants I

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Antidepressant-like effects of ferulic acid in combination with piperine: Involvement of monoaminergic system

Authors: Y. YU[1], G. LI[2], J. PANG[3], Y. XU[4], *H. ZHANG[5];
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Abstract: Ferulic acid (FA; 4-hydroxy-3-methoxy-cinnamic acid) is a main polyphenolic component of the Chinese herb Radix Angelicae Sinensis, which exhibits antidepressant-like effects through the serotonergic and noradrenergic systems. However, the potency of FA is limited in terms of antidepressant activity. The present study examined the synergistic potential of FA combined with piperine, a bioavailability enhancer, on mouse behaviors sensitive to

antidepressants, and investigated the possible mechanism. In the tail suspension and forced swimming tests (TST and FST), FA (3-180 mg/kg) alone reduced immobility with the maximal effect of only approximately 60%. Piperine, at a dose (10 mg/kg) that did not produce a significant effect on TST and FST behavior, potentiated the antidepressant-like effects of FA with the potency doubled. Consistent with the behavioral results, data from neurochemical (monoamines in the frontal cortex, hippocampus, and hypothalamus) and biochemical (monoamine oxidase, MAO) assays supported the synergistically enhanced monoaminergic function following the treatment with FA in combination with piperine. The results support the concept that the combination strategy might be an alternative therapy in treatment of psychiatric disorders with great efficacy and minimal side effects.

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Poster

773. Mood Disorders: Antidepressants I

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: NIH HL07692

NIH MH067631

VA BX11049

Title: Modified lipid raft anchoring of the G protein, Gαs subsequent to chronic antidepressant treatment, is independent of monoamine transporters but requires type 6 adenylyl cyclase (AC6)

Authors: *J. SCHAPPI, M. RASENICK;
Physiol. & Biophysics, Univ. of Illinois At Chicago, Chicago, IL

Abstract: Antidepressants of different chemical classes promote the redistribution of $G_{\alpha}s$ from lipid rafts into non-raft membrane fractions. The net result of this redistribution is increased $G\alpha_s$ coupling with transmembrane adenylyl cyclase (AC), and increased cAMP production. These changes are demonstrated via cell fractionation, functional assays, and imaging studies including FRAP (Fluorescence Recovery After Photobleaching). This phenomenon is seen in animals as well as in cell lines used in our laboratory, such as C6 glioma and PC12 pheochromocytoma. These cell lines, however, lack neurotransmitter reuptake transporters, suggesting that response to monoamine centered antidepressants entails more than inhibition of neurotransmitter reuptake

transporters or inhibition of monoamine breakdown. Furthermore, while these neural and glial cells showed an "antidepressant response", $G\alpha_s$ localization and cAMP production in kidney epithelial cells like COS1 and HEK293 were unchanged by antidepressant treatment. Similarly, membranes from liver and kidney of rats treated chronically with antidepressant did not show the same response as brain from those same animals. In this study we sought to determine whether cellular antidepressant response, with respect to increased cAMP signaling and $G\alpha_s$ localization, is dependent on the type of AC isoform expression. Cell lines lacking this $G\alpha_s$ antidepressant response, such as HEK293, become responsive after transfection with AC6. Likewise, knockdown of AC6 but not other isoforms in responsive cell lines such as C6 glioma abolishes the antidepressant response. Thus, it is suggested that AC6 performs an anchoring function for $G\alpha_s$ outside of rafts, affixing the translocated $G\alpha_s$ into the non-raft domain and facilitating an antidepressant-induced increase in adenylyl cyclase activity.

Disclosures: J. Schappi: None. **M. Rasenick:** A. Employment/Salary (full or part-time):; UIC, VA. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; VA, NIH, Eli Lilly. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Lundbeck. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pax Neuroscience. F. Consulting Fees (e.g., advisory boards); Pfizer.

Poster

773. Mood Disorders: Antidepressants I

Location: Hall A

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: Grant-in-Aid for scientific Research (C) from the Japanese Society for the Promotion of Science

Kumamoto Health Science University special fellowship (grant number 2014-C-01)

Title: GIRK2 channel KO of neurons expressing dopamine transporters mimics the effect of antitussives on the forced swimming in mice

Authors: *I. HONDA[1], K. ARAKI[2], S. HONDA[1], F. SOEDA[1], S. MISUMI[1], K. YAMAMURA[2], K. TAKAHAMA[3,4];

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Abstract: We previously reported that centrally acting antitussives inhibit G-protein-coupled inwardly rectifying potassium (GIRK) channel currents in brain neurons. In addition, these drugs at antitussive effective doses ameliorated the symptoms of animal model of various intractable brain diseases including depression. Several lines of evidence suggest that such ameliorating actions may be caused by the inhibitory action on GIRK channels coupled to dopamine receptors. In this study, therefore, we tried to generate *Girk2* conditional knockout mice and assessed depression-related behaviors of the mice. To generate GIRK2 floxed mice, we engineered the targeting vector for introducing two loxP motifs into the exon4a of Girk2 gene. Homologous recombination was induced by using CRISPR/Cas system. GIRK2 floxed mice were crossed with mice carrying the CRE recombinase gene under the control of the dopamine transporter (DAT) promoter and these mice were named GIRK2$^{DAT\ KO}$ mice (*Girk2floxed/floxed*:DAT-Cre(+)). GIRK2 floxed mice (*Girk2floxed/floxed*: DAT-Cre(-)) and DAT-Cre(+) mice (*Girk2*+/+: DAT-Cre(+)) were regarded as control mice. GIRK2$^{DAT\ KO}$ mice do not show any visibly abnormal phenotype. Their locomotor activity was comparative to that of control mice in open field test. Next, we carried out forced swimming test to assess depression-related behaviors in GIRK2$^{DAT\ KO}$ mice. GIRK2$^{DAT\ KO}$ mice significantly decreased immobility time in forced swimming test as well as effect of antitussives. These results suggest that the antidepressant-like effect of antitussives may be caused through the inhibitory actions on GIRK channel in neurons expressing DAT.

Disclosures: I. Honda: None. **K. Araki:** None. **S. Honda:** None. **F. Soeda:** None. **S. Misumi:** None. **K. Yamamura:** None. **K. Takahama:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; TAISHO PHARMACEUTICAL CO., LTD..

Poster

773. Mood Disorders: Antidepressants I

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 773.08/F26

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: VA Grant 2014

Title: Ketamine Treatment translocates G¬αs From lipid Raft Domains similar to, but on a time scale distinct from, other antidepressants

Authors: *N. WRAY, J. SCHAPPI, M. RASENICK;
physiology and biophysics, Univ. of Illinois At Chicago, Chicago, IL

Abstract: Depression is a significant public health problem for which currently available medications are often ineffective and their therapeutic effects routinely delayed by 1-2 months. We have previously shown that chronic treatment with TCA, SSRIs, and SNRIs translocate $G\alpha_s$ from lipid raft domains to associate with adenylyl cyclase and increase cAMP. We had observed this through direct assay of adenylyl cyclase, cell fractionation that showed Gsa translocating to non-raft cell membrane domains and Fluorescence Recovery after Photobleaching (FRAP). We hypothesized that Ketamine would also have a similar but rapid acting effect mimicking its quick acting effect in depressed patients. C6 cells stably -transfected with GFP-$G\alpha_s$ were treated with 10 uM Ketamine for 15 minutes and 24 hours. The cell lysates of C6 cells were collected, processed for lipid raft isolation, and subjected to Western blot analysis using antibodies to $G\alpha_s$. GFP-$G\alpha_s$- C6 cells transfected with were subjected to FRAP analysis. Both methods produced results that indicate that $G\alpha_s$ translocates from lipid raft domains. These results show that short-term treatment of ketamine creates the same antidepressant signature (translocation of Gαs from lipid rafts), as does sustained treatment with conventional antidepressants. The ability to monitor a consistent series of quantifiable measures associated with antidepressants in a simple cellular model may provide a platform to both study and develop new antidepressant compounds. Such a platform will also be able to serve as a simple detector for speed of onset of antidepressant efficacy.

Disclosures: **N. Wray:** A. Employment/Salary (full or part-time):; UIC, VA. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; VA, NIH, Eli Lilly. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PAX Neuroscience. F. Consulting Fees (e.g., advisory boards); Pfizer. **J. Schappi:** A. Employment/Salary (full or part-time):; UIC, VA. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; VA, NIH, Eli Lilly. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Lundbeck. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PAX Neuroscience. F. Consulting Fees (e.g., advisory boards); Pfizer. **M. Rasenick:** A. Employment/Salary (full or part-time):; UIC, VA. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current

grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; VA, NIH, Eli Lilly. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Lundbeck. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PAX Neuroscience. F. Consulting Fees (e.g., advisory boards); Pfizer.

Poster

773. Mood Disorders: Antidepressants I

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 773.09/F27

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: China 973 project 2013CBC31302

Title: Targeted modulation of Kv7/KCNQ channel in dopaminergic neurons of ventral tegmental area affect the neuronal excitability and behavior of depression model

Authors: L. LI, H. SUN, D. JIE, C. NIU, N. GAMPER, *X. DU, H. ZHANG;
Hebei Med. Univ., Hebei, China

Abstract: Over the years accumulated evidence implicate the mesolimbic dopamine (DA) system originating in the ventral tegmental area (VTA) in the pathogenesis and treatment of depression. The firing activity of VTA DA neurons is the key determinant in controlling the dopaminergic transmission and the depression-like behavior. Ion channels are the basic controlling components of neuronal excitability including the midbrain dopaminergic neurons, and such are the targets for new antidepressants. Kv7/KCNQ channels are voltage-dependent potassium channels composed of homo- and heteromeric complexes of five different KCNQ subunits (Kv7.1-Kv7.5, KCNQ1-5,). It has been suggested Kv7/KCNQ channels could be an important modulator of dopaminergic neuron excitability and dopaminergic transmission. Kv7.4/KCNQ4 is dominantly expressed in VTA DA neurons and presents potentially to be a target for related diseases of dopaminergic pathways. In this study we attempted to study the consequence of specific modulation of Kv7.4/KCNQ4 in VTA DA neurons, with major interests in the role of Kv7.4/KCNQ4 in DA neuron excitability and depression. Using both newly found elective activator and KCNQ4-/- mice, we first found that Kv7.4/KCNQ4 was a potent modulator of VTA DA neuron excitability in both *in vivo* and *in vitro* experiments. We further showed that Kv7.4/KCNQ4 played an important role in dopamine-induced inhibition of VTA DA activity which was mediated through auto D2 receptor and Gi/o protein pathway. Finally we found selective Kv7.4/KCNQ4 opener improved depression-like behavior of social defeat mice

model. We concluded that targeted modulation of Kv7.4/KCNQ4 K+ channels could be a new strategy for treating depression.

Disclosures: **L. li:** None. **H. Sun:** None. **D. Jie:** None. **C. Niu:** None. **N. Gamper:** None. **X. Du:** None. **H. Zhang:** None.

Poster

773. Mood Disorders: Antidepressants I

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 773.10/F28

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: AFSP

HDRF

Title: RNAseq reveals clusters of genes in the ventral dentate gyrus that induce resistance to antidepressant treatment

Authors: ***A. A. MATHE**[1], C. NASCA[2], B. BIGIO[3], V. SOUSA[4], P. SVENNINGSSON[4], B. S. MCEWEN[2];
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Abstract: The life-time depression risk is about 20 % (F>M) and yet less than 50% of affected individuals fully respond to available treatments. This prompts an imperative need to elucidate the underlying mechanisms of treatment resistance. We have focused on the glutamatergic and neuropeptide Y systems and used high-throughput analysis of gene expression changes in animal models of depression and in response to antidepressant treatments. Recently, ours and other laboratories showed that 3 days of intraperitoneal administration of the novel antidepressant acetyl-L-carnitine (LAC) induces rapid and long lasting antidepressant effects in both genetically-depressed Flinders Sensitive line (FSL) rats and following stress. Epigenetically, LAC increases expression of the metabotropic glutamate receptor, mGlu2, in the ventral DG (vDG). Here we found that LAC orally administered corrects the depressive-like phenotype of FSL, whereas, after stress exposure, LAC restored immobility time at the forced swim test only in a subset of FSL rats. These findings suggest that stress induced a resistance in the brain responses to antidepressant treatment. Thus, we employed a RNA-seq analysis of the vDG of FSL rats before/after LAC and before/after stress to shed light on the clusters of genes that

induced resistance to the antidepressant treatment. We first validated our micro-dissection approach by examining the expression of the lactate gene, which is known to be absent in the vDG. We identified ~1000 transcripts differentially expressed in three biological replicate experiments. Using pathway and GO analyses, we identified ten cohorts of transcripts. Remarkably, the largest groups of differentially expressed transcripts consisted of regulators of gene transcription, inflammatory response pathways, glutamate signaling genes, fatty acid oxidation and oxidative stress. Among the large number of genes identified by RNA-seq analysis and subsequent qPCR validation on larger biological replicate cohorts, we found that resistant FSL rats show reduced levels of the epigenetic activator of gene transcription P300, which has been recently implicated in the individual responsiveness to stress. Next-generation sequencing is providing revolutionary advances in the identification of novel candidates for therapeutic intervention. Moreover, understanding the individual differences in stress sensitivity and in the responses to antidepressant treatments may provide important knowledge for identifying markers of risk and resilience to stress that can be used to promote early intervention and develop therapeutic next-generation treatments.

Disclosures: **A.A. Mathe:** None. **C. Nasca:** None. **B. Bigio:** None. **V. Sousa:** None. **P. Svenningsson:** None. **B.S. McEwen:** None.

Poster

773. Mood Disorders: Antidepressants I

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 773.11/F29

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: VA2014

Title: Chronic antidepressants accumulate in lipid rafts and modify acylation state of the G protein, Gαs promoting translocation of Gαs from cholesterol-rich plasma membrane microdomains

Authors: S. J. ERB[1], A. CZYSZ[2,3], *M. M. RASENICK[4,5,6,1];
[1]Dept. Biopharmaceutical Sci., Univ. Illinois Col. of Pharm., Chicago, IL; [2]Neurosci. Program, [3]Med. Scientist Training Program, [4]Dept Physiol, Biophysics, [5]Dept. of Psychiatry, Univ. Illinois Coll Med., Chicago, IL; [6]Jesse Brown VAMC, Chicago, IL

Abstract: Depression is a significant public health problem for which currently available medications are often ineffective and their therapeutic effects routinely delayed by 1-2 months.

Previous studies from our laboratory have shown that: 1) Gαs, the protein that activates adenylyl cyclase, is increasingly localized to lipid rafts in depressed subjects and 2) that chronic antidepressant treatment mediates translocation of Gαs out of lipid rafts. Translocation of Gαs presents a potential mechanistic explanation for the delayed onset of therapeutic action, but the precise molecular mechanisms orchestrating Gαs translocation remain. Significant evidence suggests that localization of Gαs to the plasma membrane is facilitated through N-terminal palmitoylation, and it also appears that the localization of Gαs to lipid rafts requires palmitoylation. Gradual accumulation of antidepressants in lipid rafts and antidepressant-induced depalmitoylation of Gαs is suggested to be a causative factor in mediating translocation of Gαs to non-raft regions of the plasma membrane. We have generated stably transfected C6 glioma cells with Gαs-GFP N-terminal acylation mutants to prevent Gαs palmitoylation (Cys3Ser) or to generate Gαs that is both myristoylated and palmitoylated (Asn6Ser). The latter mutation renders Gαs,Gαi like. Both mutant Gαs-GFP constructs generate antidepressant insensitive Gαs. Furthermore, immunoprecipitation of Gαs with conformation specific nanobodies reveal that molecular partners of Gαs are influenced by Gαs acylation state and directed through chronic antidepressant treatment. These results may provide new molecular targets that allow for the discovery of novel therapies for depression.

Disclosures: S.J. Erb: None. **A. Czysz:** None. **M.M. Rasenick:** A. Employment/Salary (full or part-time):; University of Illinois at Chicago, VA Medical Center. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Veteran's Administration, NIH, Eli Lilly. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Lundbeck. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Pax Neuroscience. F. Consulting Fees (e.g., advisory boards); Pfizer.

Poster

773. Mood Disorders: Antidepressants I

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 773.12/F30

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: Fapesp

CNPq

Title: Dorsal hippocampus P2X7 and prefrontal cortex P2X4 receptor expression is modulated by stress and desipramine treatment

Authors: *D. E. RIBEIRO[1], M. A. P. SILVA[2], P. C. CASAROTTO[3], C. BIOJONE[3], S. R. L. JOCA[2];
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Abstract: There is evidence pointing a potential involvement of P2X7 (P2RX7) and P2X4 (P2RX4) receptor in mood disorders. In humans, P2RX7 polymorphism is associated to development of depression. In animal models, the lack of P2RX7 induce antidepressant-like behavior: P2RX7 KO mice exhibit antidepressant-like phenotype and systemic administration of a preferential P2XR antagonist results in antidepressant-like behavior in mice. Lastly, mice treated with a P2RX4 positive allosteric modulator induced a depressant-like behavior. Therefore, the aim of this study was to investigate if the behavioral effects induced by stress and antidepressant treatment is associated to alterations in the P2RX7 and P2RX4 expression in cortex and hippocampus, which are structures crucial to stress copying and antidepressant response. The learned helplessness model (LH) was used in order to access behavioral effects of antidepressant treatment due its good predictive and face validity. LH is a classical and widely used model of depression based on the observation that exposure to uncontrollable stressors induces behavior deficits. Adult male rats were submitted to LH pre-test session (40 inescapable footshocks: 0.4 mA, 10 s duration, 30-90 s interval) and were treated with vehicle or desipramine 25 mg/kg (DES) for seven days, and were tested 1 hour after the last injection. The test session consisted of 30 escapable footshocks (0.4 mA, 10 s duration, 30-90 s interval) preceded by a tone (60dB, 670Hz) that started 5s before each shock and lasted until its end. Animals could avoid the shock during sound presentation or interrupt its presentation by crossing to the opposite side of the chamber (escape). Absence of one of these behaviors was considered an escape failure. An independent group of rats was submitted to LH pre-test session (stressed group) or habituation in the same apparatus (non-stressed group), and then the rats were treated with vehicle or DES for seven days, and killed 1 hour after the last injection in order to have their prefrontal cortex and hippocampus dissected. P2RX7 and P2RX4 expression in prefrontal cortex and hippocampus was determined by western blotting. DES treatment decreased the number of escape failures of rats submitted to the LH paradigm ($t_{17}= 3.16$; $p<0.05$). The animals submitted to LH pretest session showed an increase in the dorsal hippocampus P2RX7 expression ($F_{2,14}=7.282$; $p<0.05$) and a decrease in the prefrontal cortex P2RX4 expression ($F_{2,16}=4.560$; $p<0.05$). These effects was prevented by the DES treatment. Therefore the purinergic signaling can be involved in stress response and antidepressant treatment.

Disclosures: **D.E. Ribeiro:** None. **M.A.P. Silva:** None. **P.C. Casarotto:** None. **C. Biojone:** None. **S.R.L. Joca:** None.

Poster

773. Mood Disorders: Antidepressants I

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 773.13/F31

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: Institut de Recherches Internationales SERVIER, Suresnes, France

Title: Agomelatine reverses the behavioral deficits and the reductions in synaptic, GABAergic and glial makers induced by chronic unpredictable stress in the rat prefrontal cortex

Authors: *M. BANASR[1], M. THOMAS[1], A. LEPACK[1], G. SANACORA[1], R. DUMAN[1], C. GABRIEL[2], E. MOCAER[2];
[1]Dept Psychiatry, Yale Univ., New Haven, CT; [2]Inst. de Recherches Internationales SERVIER, Suresnes, France

Abstract: Growing evidence demonstrate that drastic morphological and cellular changes occurs in the limbic brain regions of patients with MDD. Post-mortem studies report anomalies of GABAergic neurons function, reduced astrocyte number and neuronal atrophy of pyramidal neurons in the prefrontal cortex (PFC) of MDD patients. Using the chronic unpredictable stress (CUS) paradigm, we previously demonstrated that chronic stress induces depressive-like behavioral deficits as well as molecular changes similar to the cortical alterations reported with human depression. Here, we used this model to test the therapeutic efficacy of agomelatine, a novel antidepressant acting as a melatonergic receptor agonist and serotonergic (5-HT2C) receptor antagonist at both the behavioral and cellular level. Adult Sprague-Dawley rats were subjected to CUS (2 stressors/day) for 35 days. For the last 3 weeks of the CUS exposure, animals were injected with agomelatine (40mg/kg, i.p) or fluoxetine (5mg/kg, i.p). At the end of the experiment, animals (6 groups, n=8 per group) were tested in the sucrose preference test and in the novelty suppressed feeding test. We found that treatment with agomelatine or fluoxetine increased sucrose preference and decreased latency to feed in animals subjected to CUS, demonstrating that agomelatine or fluoxetine treatment reversed CUS-induced anhedonia- and anxiety-like deficits. At the cellular level, we examined the effects of chronic treatment with agomelatine or fluoxetine on the expression levels of key protein involved in the function GABAergic neurons, astrocytes or synaptic plasticity using western blot analysis. Preliminary data suggest that chronic treatment with agomelatine blocked the CUS-induced reductions of the expression of phospho/total mTOR (-29%), PSD95 (-20%), Synapsin-1 (-29%), GAD67 (-21%), GLT1 (-15%) and GFAP (-19%) in the PFC. Chronic treatment with fluoxetine also reversed these effects. Further studies examining the effects of agomelatine on CUS-induced changes in

protein expression in the dorsal and ventral hippocampus are underway. Altogether our results confirmed the antidepressant-like efficacy of chronic treatment with agomelatine as indexed by reversal of stress-induced anhedonia- and anxiety-like deficits and suggest that prevention of key cellular changes associated with synaptic loss and cortical GABAergic and astrocytic dysfunction contribute to the antidepressant action of agomelatine. Further studies will be needed to evaluate the kinetics of the improvement for each antidepressant.

Disclosures: **M. Banasr:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; This work was supported by the Institut de Recherches Internationales SERVIER, Suresnes, France.. **M. Thomas:** None. **A. Lepack:** None. **G. Sanacora:** None. **R. Duman:** None. **C. Gabriel:** A. Employment/Salary (full or part-time):; IRIS. **E. Mocaer:** A. Employment/Salary (full or part-time):; IRIS.

Poster

773. Mood Disorders: Antidepressants I

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 773.14/F32

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: MNiSW/NCN Grant UMO-2012/07/B/NZ4/01811

Title: Imipramine affects circulating BDNF, prolactin and ACTH in time dependent manner

Authors: ***M. KUSMIDER**, A. FARON-GÓRECKA, J. SOLICH, J. WÓJCIKOWSKI, D. ZURAWEK, P. PABIAN, W. DANIEL, M. DZIEDZICKA-WASYLEWSKA;
Pharmacol., Inst. of Pharmacol. P.A.S., Krakow, Poland

Abstract: Antidepressant action requires time for improvement to appear. Usually several weeks of treatment are needed to see mood stabilization. The biological psychiatry can’t explain this phenomenon as yet. Several theories address this, with the most recognized neurotrophin/neuroplasticity theory, with BDNF as the core molecule. The present data are connected with two clinical situations: so called compliance, linked with effectiveness/adverse effects ratio, and the antidepressant discontinuation syndrome. Our research focus on changes in rat nervous system following single and chronic antidepressant administration, changes that appear as the function of time. The study was performed on male rats, of Wistar HAN strain. The experiments were carried out with accordance to bioethical committee of Institute of

Pharmacology PAS. For 20 days animals were receiving daily i.p. injections with saline (SAL 2ml/kg) or Imipramine (IMI 10mg/kg/2ml). On 21st day half of animals treated previously with saline received singledose of IMI 10mg/kg i.p. Therefore, since that day, we had 3 groups of animals: receiving SAL, IMI chronically, and IMI once. Next, animals have been left with no additional treatment for next 21 days. During that time, at certain time points (3h, 72h, 7days and 21days after last injection) 5 animals of each group were sacrificed and plasma, serum and brain tissue was collected for further analysis. HPLC analysis of plasma samples revealed that IMI and its metabolite, desipramine, were present in samples only 3h after last injection, at the 72h and next time points the analytes were undetectable. Plasma and serum concentrations of BDNF, prolactin (PRL) and ACTH were detected by the means of Luminex technology. Chronic IMI treatment tended to flatten the natural differrence between plasma and serum concentration of BDNF (the neurotrophin is released from platelets during clotting). During discontinuation we observed oscillations in BDNF concentrations in both IMI-chronic, and IMI-once groups, reaching the highest levels at the 21st day. PRL and ACTH, which we considered as the indicators of stress have been elevated at 72h and 21days of drug discontinuation, but only in a group treated with IMI chronically. The most important conclusion we made is that the elevation of BDNF plasma level could be achieved not only with the IMI presence in the animal, but also after couple of weeks of drug discontinuation.

Disclosures: M. Kusmider: None. **A. Faron-Górecka:** None. **J. Solich:** None. **J. Wójcikowski:** None. **D. Zurawek:** None. **P. Pabian:** None. **W. Daniel:** None. **M. Dziedzicka-Wasylewska:** None.

Poster

773. Mood Disorders: Antidepressants I

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 773.15/F33

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: The regulation mechanism of miR-16 on serotonin related neural circuits through PI3K signaling pathway in Chronic Mild Stress rats model

Authors: Z. HU[1], *M. FANG[2], Y. YANG[2];
[1]Dept. of Obstetrics and Gynecology. Hangzhou Red Cross Hosp., Hangzhou, China; [2]Zhejiang Univ., Zhejiang, China

Abstract: The pathogenesis of depression is generally recognized as dysfunction of the serotonin system. Recently, miR-16 has been discovered to affect function of the serotonin transporter in

antidepressant drugs. Our study aims to explore the molecular mechanism of miR-16 on the structure and function of 5-HT related neural circuits. 5-HT and miR-16 inhibition was employed, and changes were analyzed with optogenetics tools combined with magnetic resonance imaging, fluorescent tracer technique and molecular biological methods. From our previous results, stressed rats showed typical symptoms of depression, atrophy appeared in the hippocampus and amygdala neurons, reduced number of dendritic spines and changed their morphology. There were also obvious changes in cytoskeleton protein expression. Seven days after MiR-16 lentivirus injection, RT-PCR and Western Blotting were used to examine the mRNA and protein expression of key proteins in PI3K signaling pathways in the hippocampus, including MiR-16, 5-HTT, 5-HT2a, mTOR, AKT, P-AKT, PI3K. And the results indicated that expressions in the miR-16 group were higher than the CMS (chronic mild stress) group in both mRNA and protein levels. Results from behavioral experiments also revealed the similar phenomenon. The sucrose consumption test and open field test were chosen to detect depression like behavior at the time points of seven days pre and post injection. The MiR-16 group appeared to have a higher sucrose intake rate and mobile number than the CMS group. Therefore, we concluded with a hypothesis that miR-16 could play a role in 5-HT related neural circuits and anti-depressive roles through hippocampal PI3K signaling pathways.

Disclosures: **Z. Hu:** None. **M. Fang:** None. **Y. Yang:** None.

Poster

773. Mood Disorders: Antidepressants I

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Program#/Poster#: 773.16/F34

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: MH038752

MH090236

MH104656

NARSAD

Title: Ketamine-induced inhibition of glycogen synthase kinase-3 contributes to the augmentation of AMPA receptor signaling

Authors: ***S. GRIECO**[1,2], C. AMADEI[2], K. DOWNEY[2], R. JOPE[2,1], E. BEUREL[2,1]; [1]Biochem., [2]Univ. of Miami, Miami, FL

Abstract: Sub-anesthetic doses of ketamine have been found to provide rapid antidepressant actions, indicating that the cellular signaling systems targeted by ketamine are potential sites for therapeutic intervention. Ketamine acts as an antagonist of N-methyl-D-aspartate (NMDA) receptors, and animal studies indicate that subsequent augmentation of signaling by α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors is critical for the antidepressant outcome. Here we tested if the inhibitory effect of ketamine on glycogen synthase kinase-3 (GSK3) affected hippocampal cell-surface AMPA receptors. Treatment with an antidepressant dose of ketamine increased the hippocampal membrane level of the AMPA receptor GluR1 subunit, but did not alter the localization of GluR2, GluR3, or GluR4. This effect of ketamine was abrogated in GSK3 knockin mice expressing mutant GSK3 that cannot be inhibited by ketamine, demonstrating that ketamine-induced inhibition of GSK3 is necessary for up-regulation of cell surface AMPA GluR1 subunits. AMPA receptor trafficking is regulated by PSD95, a substrate for GSK3. Ketamine treatment decreased the hippocampal membrane level of phosphorylated PSD-95 on Thr-19, the target of GSK3 that promotes AMPA receptor internalization. These results demonstrate that ketamine-induced inhibition of GSK3 causes reduced phosphorylation of PSD-95, diminishing the internalization of AMPA GluR1 subunits to allow for augmented signaling through AMPA receptors following ketamine treatment.

Disclosures: S. Grieco: None. **C. Amadei:** None. **K. Downey:** None. **R. Jope:** None. **E. Beurel:** None.

Poster

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Program#/Poster#: 773.17/F35

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: AFSP

HDRF

Title: xCT epigenetically promotes homeostatic regulation of the glutamate system in the responses to stress: implications for next-generation treatments

Authors: *D. A. ZELLI, B. S. MCEWEN, C. NASCA;
Neuroendocrinology, The Rockefeller Univ., New York, NY

Abstract: Stress acts synergistically with excitatory amino acids to induce either protective or damaging effects on the brain, and dysregulated glutamate homeostasis has been associated with several psychiatric and neurological disorders. Glutamate genes present logical targets to develop novel therapeutic strategies with a rapid onset of action. Previous studies have shown rapid antidepressant effects of either ketamine, which blocks NMDA receptors, or acetyl-L-carnitine (LAC), which up-regulates mGlu2 via acetylation of histone H3 on lysine 27. Preliminary data from our laboratory reveal that chronic restraint stress (CRS) results in susceptible individuals in anxiety and depressive-like phenotypes at the light dark and forced swim test, respectively. Molecularly, CRS mice have reduced hippocampal levels of the xCT exchanger, which facilitates cystine uptake into glial cells in exchange for glutamate to the extracellular space, along with decreased levels of the presynaptic inhibitor of glutamate release, mGlu2 receptors, which have been recently identified as biomarkers of individual susceptibility to stress and antidepressant treatments. Sub-regionally, CRS-induced xCT-mGlu2 changes appear to be localized to the ventral dentate gyrus (vDG). We also found that 3-days of oral treatment with the acetylating agent N-acetyl-cystine (NAC) increases xCT expression in the vDG while also increasing mGlu2 levels in the same sub-region and this corrects the behavioral abnormalities induced by CRS more rapidly than spontaneous recovery and treatment with the SSRI, fluoxetine. Moreover, we found that, in parallel with the results described above on the CRS-induced transcriptional down-regulation of xCT expression in the vDG, CRS decreases levels of the transcriptional activator P300 in the vDG and this deficit is corrected by NAC treatment. These findings reveal a previously unknown role for xCT in a homeostatic regulation of the vDG in the stress responses in relation to anxiety and depressive-like behaviors and antidepressant action. Together, our results have implications for disorders in which glutamatergic transmission is dysregulated, revealing that prolonged stress can produce potentially maladaptive neural and behavioral responses that can be corrected by novel epigenetic therapies, such as the acetylating agent NAC and L-acetylcarnitine, targeted to promote resilience by producing compensatory mechanisms.

Disclosures: **D.A. Zelli:** None. **B.S. McEwen:** None. **C. Nasca:** None.

Poster

773. Mood Disorders: Antidepressants I

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 773.18/F36

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: AFSP

HDRF

Title: Stress induced elongation of pyramidal, but not stellate, neurons in the basolateral amygdala with implications for next generation treatment

Authors: ***T. LAU**[1], B. BIGIO[2], D. ZELLI[1], B. S. MCEWEN[1], C. NASCA[1];
[1]Neuroendocrinology, [2]Ctr. for Clin. and Translational Sci., The Rockefeller Univ., New York, NY

Abstract: The hippocampus is a target of stress and stress hormones. Structural and functional hippocampal changes have been associated with the onset and exacerbation of psychiatric disorders, such as depression and anxiety. Stress effects on the brain, however, are not exclusive to the hippocampus but they also involve the amygdala which is increasingly recognized as a target of stress. Additionally, there are emerging evidence showing the ventral hippocampus, which projects to the amygdala, to be a target of stress hormones and antidepressants with functions and connectivity that are distinct from the dorsal hippocampus. Here we examined the effects of chronic stress on the amygdala by subjecting C57BL/6N mice to 21 consecutive days of chronic restraint stress (CRS) and then we examined neuron morphology within the subregions of the amygdala. Behavioral assessments were carried out using the forced swim and light dark test 24 hours after the last episode of stress to measure depression and anxiety-like levels, respectively. Mice were sacrificed shortly after the behavioral assessments. An additional group of stressed mice was treated orally with the novel antidepressant L-acetylcarnitine (LAC) for 3 days. The extracted brains were then processed using the Rapid Golgi Staining Kit. Amygdala neurons were distinguished as pyramidal or stellate based on their morphology. Results revealed that pyramidal neurons from CRS animals exhibited greater total dendritic length compared to unstressed control mice. Furthermore, the dendrites from the stressed group were more elaborate at a closer distance to the soma compare to the control group, showing greater dendritic lengths and more intersections. Interestingly, LAC treatment corrected CRS-induced mood abnormalities, but, LAC treated mice also showed an even greater dendritic length compare to both control and stress groups, suggesting that a counter-regulatory mechanism may be involved in the fast antidepressant effects of LAC. The number of intersections for each group correlated in a similar pattern where the stress group displayed more intersections compare to the control group but with the LAC group showing the highest number of intersection. In contrast, little effect of CRS was seen in the BLA stellate neurons and in the lateral amygdala neurons. At present, RNAseq is underway to understand the clusters of genes that mediated stress effects in the amygdala. These results underscore the importance of better understanding how stress induces structural and functional changes in higher-level cognitive brain regions with implication for the development of drugs with better profiles of efficacy and tolerability.

Disclosures: **T. Lau:** None. **B. Bigio:** None. **D. Zelli:** None. **B.S. McEwen:** None. **C. Nasca:** None.

Poster

773. Mood Disorders: Antidepressants I

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Support: MH064756

MH086108

Brain & Behavior Research Foundation

Shirley and Stefan Hatos Foundation

UCLA Weil Endowment Fund

Title: Sex- and sert-associated differences in stimulated serotonin neurotransmission revealed by fast microdialysis

Authors: *H. YANG[1], M. M. SAMPSON[2], D. SENTURK[3], A. M. ANDREWS[4];
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Abstract: *In vivo* microdialysis is widely used to study neurotransmitter levels in the brain to determine how they respond to biological challenges. We combined our recent improvements in the temporal resolution of online serotonin sampling with a brief K+ stimulus paradigm to investigate evoked serotonin release. Mice with constitutive loss of serotonin transporter (SERT) expression and wildtype littermates were assigned to one of five groups: (1) wildtype male (N=7); (2) wildtype male with acute serotonin-selective reuptake inhibitor (SSRI) escitalopram (ESC) perfusion (N=8); (3) SERT knockout male (N=6); (4) wildtype female metestrus/diestrus (N=5); and (5) wildtype female proestrus/estrus (N=5). Estrous phase was determined by vaginal smear immediately after the completion of dialysis. We observed stimulated serotonin overflow with 120 mM K+ pulses as brief as 1 min in conjunction with 2 min online dialysate sampling and analysis in ventral striatum. After 1-min K+ stimulation, all wildtype male subjects exhibited detectable stimulated serotonin overflow. By contrast, 5/8 ESC-treated males and one each from the other groups failed to respond to the 1-min high K+ stimulus. Stimulated serotonin levels in female mice during the high estrogen period of the estrous cycle (proestrus/estrus) were similar to serotonin levels in male wildtype male mice (1-5 min stimuli). By contrast, stimulated serotonin overflow during the low estrogen period in female mice (metestrus/diestrus) was

elevated to the same extent as in male wildtype mice with local SERT inhibition by ESC. Stimulated serotonin levels in knockout mice were considerably higher than all other groups throughout the stimulation paradigm. We conclude from the latter that serotonin release is greatly potentiated as a result of life-long loss of SERT. After repeated maximal stimulation (6-min stimuli), evoked serotonin overflow decreased only in groups with the highest levels of stimulated overflow (i.e., SERT knockout, wildtype with acute local ESC-treatment, and female during the metestrus/diestrus) at shorter inter-stimulus intervals. When combined with brief K+ stimulation, fast microdialysis enables dynamic changes in serotonin transmission associated with normal female hormonal cycles, and pharmacologic compared to genetic loss of SERT function to be delineated.

Disclosures: H. Yang: None. **M.M. Sampson:** None. **D. Senturk:** None. **A.M. Andrews:** None.

Poster

773. Mood Disorders: Antidepressants I

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: Hundred Talent Program of Chinese Academy of Sciences (ZW)

Title: The key targets of antidepressants revealed by functional brain connectome analysis in macaques

Authors: Q. LV[1], J. PU[1], G. LI[2], Z. WANG[1], Z. SHEN[1], Q. JIANG[1], L. YANG[1], Z. XUE[2], H. HU[1], *Z. WANG[1];
[1]Inst. of Neurosci., Shanghai, China; [2]Dept. of Anesthesiology, Zhongshan Hosp., Shanghai, China

Abstract: Most antidepressants currently available to clinical patients usually require weeks to take effect, and only limited number of patients with depression achive alleviation to lesser or greater extents. Growing studies have consistently demonstrated that a single-dose of N-methyl-D-aspartate (NMDA) antagonist ketamine produces rapid (within hours) antidepressant response, even in patients with treatment-resistant depression. Although numerous studies have focused on uncovering the underlying molecular mechanisms, identifying the key brain areas preferentially targeted by two types of antidepressants may provide novel insights into development of efficacious pharamacological therapy. Here we combined the resting-state functional magnetic

resonance imaging (fMRI) and graph theoretical analysis to quantitatively assess the brain regions influenced by sertraline and ketamine. Fifteen healthy macaque monkeys were involved, and received a single-dose administration of ketamine (0.5 mg/kg, n=9), sertraline (5mg/kg, n=11) and saline (n=9) as control. The interval between two experimental conditions was spaced at least one month to avoid carry-over effects. Resting-sate fMRI data were acquired in anesthetized animals on a Siemens Trio 3T scanner with an enhanced gradient insert AC88. To maximize the antidepressant effects on the brain network, scans were scheduled ~18 hours and ~4 hours after the administration of ketamine and sertraline, respectively. We observed large-scale decreased functional connectivity caused by sertraline and ketamine compared to the saline group. Specifically, network based analysis showed that a single-dose of ketamine and sertaline both modulated extensive connections with nucleus accumbens (NAc) and subgenual anterior cingulate cortice (sgACC) ($p < 0.05$, corrected). In contrast with the sertraline group, ketamine intake down-regulated the functional connectivity between dorsal prefrontal cortex (dPFC), superior temporal gyrus and putamen ($p < 0.05$, corrected). This finding suggests that dPFC, superior temporal gyrus, putamen together with NAc and sgACC may represent the key target brain regions to achieve rapid and efficacious antidepressant effects.

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Poster

773. Mood Disorders: Antidepressants I

Location: Hall A

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Program#/Poster#: 773.21/F39

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Acupuncture decreases dendritic arborization and dendritic spine density in basolateral amygdala in social isolated rats

Authors: ***A. DAVILA HERNANDEZ**, M. DEL ANGEL-MUÑOZ, S. ZAMUDIO, C. CAMPOS-RODRIGUEZ, R. GONZALEZ-GONZALEZ, E. RAMIREZ-SAN JUAN;
Inst. Politecnico Nacional, Mexico, Mexico

Abstract: Introduction: Depression is one of the most common psychiatric disorders; it displays high rates of lifetime prevalence, early age of onset, high chronicity, and social role impairment, and is characterized by a depressed mood and anhedonia. It is associated to neuromorphological changes in some structures, such as: hipoccampus and amygdala related to severity of symptoms. Due the importance of depression and undesirable effects of conventional treatment, is necessary

to use complementary therapies such as acupuncture, a non-pharmacological treatment, simple procedure and, without adverse effects, which has demonstrated clinical efficacy in depression, and using embedding thread in acupoints can be a prolonged stimulus for at least three weeks. Objective: to evaluate the effect of embedding thread in acupoints on pyramidal neurons morphology in the basolateral amygdala of social isolated rats (a depression model). Methods: 60 Sprague-Dawley male rats were used and randomly divided in six groups, with 10 rats each: a control group, social isolated group (SI), social isolated + embedding thread group (SI+AC), social isolated + sham embedding thread group (SI+sham), social isolated + fluoxetine group (SI+FX), and social isolated + vehicle group (SI+VH). Animals were weaned on postnatal day (PD) 21 and submitted to social isolation for eleven weeks, the control group was housed in social conditions. On PD 77, the SI+AC was anesthetized with sodium pentobarbital (28 mg/kg) and embedded thread in acupoints (BL15, BL18, BL21, BL23, Du20 and, Ex 3). The sham group was punctured without embedded thread, the SI+FX was subcutaneously treated with fluoxetine (2 mg/kg/day) during the following 21 days, the SI+VH received saline solution. After the treatments, the animals were sacrificed by overdose of sodium pentobarbital and perfused intracardially with 0.9% saline solution. The brains were removed, processed by the Golgi-Cox stain and analyzed by the Sholl method. Results: The dendritic morphology study showed that the social isolated animals presented an increase in dendritic length of pyramidal cells from basolateral amygdala, acucatgut (SI-AC) induced a reduction in dendritic length, at the same level of control group, and, acucatgut or treatment with fluoxetine also decreased the density of dendritic spines, although in the SI+FX did not reach the level of the control group. Conclusions: 1. Social isolation in rats induces dendritic morphology changes in basolateral amygdala, similar to those that have been observed in patients with first episode of depression. 2. Embedded thread in acupoints reversed the neuromorphological effects of social isolation.

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Poster

773. Mood Disorders: Antidepressants I

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Program#/Poster#: 773.22/F40

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: AFSP

HDRF

Title: Glucocorticoids-IL6 crosstalk allows identification of inherent individual differences that predict and promote vulnerability to social stress

Authors: *B. S. MCEWEN[1], C. NASCA[1], G. E. HODES[2], V. KANA[2], E. J. NESTLER[2], S. J. RUSSO[2];
[1]Lab. of Neuroendocrinology, The Rockefeller Univ., New York, NY; [2]Dept. of Neurosci. and Friedman Brain Inst., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Stressful experiences superimposed on top of inherent individual differences can lead susceptible individuals to develop debilitating mental and physical diseases, whereas other individuals are resilient and show cognitive flexibility to the same stressor. Recently, we introduced a rapid screening method for identifying susceptible individuals among an inbred population of mice. Individuals that show increased expression of hippocampal mineralocorticoid receptors (MR), before any applied stress, display increased levels of anxiety- and depressive-like behaviors after exposure to stress along with reduced levels of the presynaptic inhibitor of glutamate release, mGlu2 receptors. Here, we tested whether individual differences in hippocampal MR expression correlate with inherent differences in the peripheral immune system that have been shown to predict and promote vulnerability to social defeat stress (SDS). Previous studies found that mice with higher levels of IL-6 released from leukocytes following *ex vivo* LPS stimulation prior to stress, show low levels of social interaction after chronic SDS. Using the light-dark test (LD), we screened an inbred population of C57bl6 male mice and obtained leucocyte profiles along with IL-6 levels at baseline and from *ex vivo* stimulated leukocytes before applying chronic SDS. We found that mice identified as high susceptible in the LD show higher prestress levels of circulating Ly6chi monocytes and more IL-6 release when stimulated *ex vivo* with LPS and before any applied stressor. No difference in IL-6 without LPS stimulation was found. Furthermore, the peripheral leukocyte profiles show no difference in the Cd45 leukocyte population but a slight increase in neutrophils in susceptible mice compared with resilient mice, suggesting that prestress increased IL-6 levels are largely due to the Ly6chi monocytes and neutrophil populations. These results show that mice prone to develop a susceptible phenotype had higher hippocampal levels of MR and greater IL-6 release following *ex vivo* stimulation with LPS. Together, our findings suggest that the LD and hippocampal MR levels are features that connect with the vulnerability to social defeat stress as well as other stressors, providing tools to screen for inherent differences in the susceptibility to develop stress-related mood disorders. Moreover, the correlation between peripheral markers of inflammation (like IL-6) and LD (which identifies individuals with higher hippocampal MR) may offer the opportunity to develop prophylactic therapeutic strategies, pharmacological or behavioral, to prevent the deleterious effects of stress in susceptible individuals.

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Poster

773. Mood Disorders: Antidepressants I

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Program#/Poster#: 773.23/F41

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: funding from the University of Dayton

Title: Ketamine elicits sex-dependent rapid and sustained neurobehavioral effects in C57BL/6J mice

Authors: *C. THELEN[1,2], J. SENS[2], A. FRANCESCHELLI[2], P. M. PITYCHOUTIS[2];
[1]Biol., The Univ. of Dayton, Dayton, OH; [2]Biol. and Ctr. for Tissue Regeneration & Engin. (TREND), Univ. of Dayton, Dayton, OH

Abstract: An exciting discovery in the field of modern neuropsychopharmacology was the finding that a single sub-anesthetic dose of the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine can induce both rapid and sustained antidepressant-like effects in treatment-resistant depressed patients and in animal models of depression. Despite the progress made in the identification of the behavioral and neurobiological mechanisms underlying the antidepressant-like effects of ketamine, knowledge regarding its effects in the female sex is limited. In the present study, male and female C57BL/6J mice were administered increasing doses of ketamine (i.e. 3 mg/kg, 5 mg/kg, 10 mg/kg) or saline (0.9% NaCl). The rapid and sustained antidepressant- and anxiolytic-like behavioral effects of ketamine were assessed in the forced swim test (FST) and the novelty-suppressed feeding (NSF) test at 30 min, at 24 h or at 7 days post-administration. In our experimental setup, female mice responded to lower doses of ketamine than males in the FST, at 30 min and at 24 h, while no effects were evidenced in the NSF test. Importantly, only the highest dose of ketamine (i.e. 10 mg/kg) induced both rapid and sustained antidepressant-like effects in both sexes in the FST and thus was subsequently selected for neurochemical estimations. Mice of both sexes were administered ketamine (10 mg/kg) or saline and were sacrificed at 30 min (rapid effects) or at 24 h (sustained effects) post-injection. Neurochemical analysis of monoamines (i.e. serotonin, dopamine and their metabolites) and excitatory amino acids (glutamate and aspartate) was performed with high performance liquid chromatography (HPLC) in brain regions implicated in the neurobiology of major depression. According to our data, ketamine induced sex-dependent dopaminergic alterations in the nucleus accumbens and also affected cortical and hippocampal excitatory amino acids in a sex-specific manner. These findings highlight the critical role of sex in the manifestation of antidepressant-like neurobehavioral responses to ketamine in mice.

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Poster

773. Mood Disorders: Antidepressants I

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: ANR

Title: Resistance to chronic antidepressant treatment: a behavioural and neurogenic study in a neuroendocrine-based mice model of anxiety/depression

Authors: ***M. MEKIRI**, A. M. GARDIER, D. J. DAVID, J.-P. GUILLOUX;
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Abstract: Major depressive disorder (MDD) is a major and highly debilitating disease. Despite major improvements in the field of antidepressant drug treatments, MDD still suffers from a low rate of treatment response, as 60% of MDD patients do not respond adequately to pharmacological treatment. Moreover, resistance to antidepressant treatment, which refers to an inadequate response to two consecutive treatments with drugs having a different pharmacological mechanism of action (1), occurs in ≈30% of patients. Although preclinical studies suggest that suppressing adult hippocampal neurogenesis impacts part of the effects of chronic antidepressant, yet no study observed a lack of antidepressant drug response associated with altered neurogenesis. Moreover, β-arrestins proteins levels in peripheral blood mononuclear cells (PBMC) are altered in the MDD subjects and restored after antidepressant drug treatment (2). Yet, we do not know if alterations of proteins expression involved in the β-arrestin pathway are associated with non-response to antidepressant drugs. Here, we studied non-response and resistance to antidepressant drugs in a neuroendocrine mouse model of anxiety/depression based on a chronic corticosterone administration (35 µg/ml, p.o., for 4 weeks). Emotionality score in CORT-treated mice was assessed using various behavioural tests (3). In a translational manner, response in mice was defined as a 50% decrease in initial emotionality score. CORT-treated animals display a higher z-score than control mice. Fluoxetine was then administered (18 mg/kg/j, p.o., for 4 weeks), and non-responder mice (≈30%) were switched to chronic imipramine administration (40 mg/kg, p.o., 4 weeks). About 30% of mice did not respond adequately to both therapeutic strategies and were characterized as “treatment-resistant” mice. Animals showing lack of treatment response displayed altered neurogenesis in the dentate gyrus

of the hippocampus, with lower cell survival, decreased neuronal maturation and lower dendritic arborization compared to responder mice. We isolated PBMC from the blood of these mice to assess whether non-response to treatment is associated with alterations of proteins involved in the β-arrestin pathway. Overall, our results support that treatment resistance is observable in an animal model of the disease, and that impaired response to antidepressant drug treatment is associated with altered hippocampal neurogenesis in adult mice. (1) Nierenberg and DeCecco, 2001 (2) Connolly and Thase, 2011 (3) Guilloux, J. P. and al. 2011

Disclosures: **M. Mekiri:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; ANR (National Agency of Research). **A.M. Gardier:** None. **D.J. David:** None. **J. Guilloux:** None.

Poster

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NIH Grant T32 DK059803

Title: 'Sequester stress': the development of a novel animal model for life stress and a depression-like phenotype

Authors: *B. L. KOPP[1], C. LYONS[2], B. MYERS[1], M. B. SOLOMON[1], J. P. HERMAN[1], *F. CORREA[2];
[1]Psychiatry and Behavioral Neurosci., [2]Summer Undergraduate Res. Fellowship Program, Univ. of Cincinnati, Cincinnati, OH

Abstract: Chronic exposure to stressors is frequently used to model a depression-like phenotype in rodents. Significant loss often triggers depressive episodes in humans, and currently there are no rodent models that emphasize loss to induce long-term stress. To this end, we developed "sequester stress" as a novel and potentially translational model of stress and depression-like

characteristics. Sequester stress entails exposing adult male Sprague Dawley rats to environmental enrichment for 1 month and subsequently removing them from enrichment for 2-3 weeks, to model the removal of a positive stimulus rather than the application of a negative experience. Environmental enrichment consists of 10 rats per 1mm3 cage, with wire mesh walls for climbing and novel toys rotated in every week. Upon sequestration, rats are placed into standard single housing. In comparison to both single housed controls and continuously enriched controls, the enrichment sequestered rats (ES) have increased immobility in the forced swim test (FST), increased body weight gain, blunted corticosterone and ACTH responses to a novel stressor, and increased initial sucrose consumption. Antidepressant treatment with imipramine reverses the FST and body weight phenotypes. Although rewarding, environmental enrichment increases corticosterone and ACTH responses to stress and decreases body weight gains. Therefore, we compared the effect of ES with other regimens that cause prolonged stress activation, repeated restraint and chronic variable stress. The ES phenotype was specific to enrichment deprivation, and does not generalize to loss of chronic habituating or unpredictable stress. Furthermore, we test whether the exclusive loss of the social component or exercise component of environmental enrichment is sufficient to produce the phenotype. Together, our studies indicate that the sequester model produces a novel and robust rodent phenotype, addressing symptoms of 'atypical' depression, which include hyperphagia, weight gain, and hypothalamo-pituitary-adrenocortical axis suppression.

Disclosures: **B.L. Kopp:** None. **C. Lyons:** None. **B. Myers:** None. **M.B. Solomon:** None. **J.P. Herman:** None. **F. Correa:** None.

Poster

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: MNiSW/NCN Grant UMO-2012/07/B/NZ4/01811

Title: Effect of imipramine on the peripheral th2/th1 cytokine production in the rat serum in the time-dependent sensitization paradigm

Authors: *A. FARON-GÓRECKA, M. KUśMIDER, J. SOLICH, P. PABIAN, D. ŻURAWEK, B. ZEMłA, M. DZIEDZICKA-WASYLEWSKA;
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Abstract: Time-dependent sensitization (TDS) has been described in animal models over the past 40 years (Antelman et al., 2000). It is a phenomenon that occurs in a variety of biological systems, and corresponds to the cellular and systems response to a foreign or stressful stimulus. The exposure to the stimulus triggers the responses typical of that particular biological system, which are progressively amplified with time. This phenomenon has potential major implications for clinical pharmacology. Antidepressant action also may be a fruitful paradigm to understand the relevance of TDS for psychopharmacological treatment. Our previous results confirm this hypothesis – we have shown that the shortening of immobility time in the forced swim test induced by a single dose of imipramine (IMI) persisted throughout the whole experimental period (21 days) and was similar to that seen in a group of animals treated repeatedly (21 days) with the drug (Kuśmider et al., 2006). There are data implicating the inflammatory theory of depression (e.g. higher levels of inflammation increase the risk of depression, remission of clinical depression is often associated with a normalization of inflammatory markers), therefore we tried to correlate the TDS paradigm using IMI treatment with immunological theory of depression. In our experimental studies, using Luminex Technology, we measured the peripheral th2/th1 cytokine production (BioRad Assay) in the serum of rats treated with IMI (10 mg/kg) chronically (21 days, 21x) and rats treated with single dose of IMI (1x) at the beginning and remained in the experiment free of further drug administration for next 20 days. During that time, at certain time points (3h, 72h, 7days and 21days after last injection) 5 animals of each group were sacrificed and plasma, serum and brain tissue was collected for further analysis. All experiments were carried out in accordance with Bioethical Committee at the Institute of Pharmacology, Polish Academy of Sciences, Krakow, Poland. The study was performed on male rats, of Wistar HAN strain. After 3 h following IMI treatment a th1 shift was observed in both groups: treated chronically and with single dose of IMI ($p<0.05$ vs control group). After 72h and 7 days no changes in th2/th1 shift were observed, only after 21 days in animals chronically receiving IMI, th2 shift was observed. In addition, after 7 days of IMI withdrawal, the changes in cytokines: IL10, IL1alfa, IL12, IL-5 were similar in both groups (1x and 21x of IMI). Our results do not suggested directly the correlation between TDS paradigm and immunological theory of depression, however some data (e.g. those observed after 7 days) may indicate this relationship.

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Poster

773. Mood Disorders: Antidepressants I

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: Whitehall Foundation

Title: FosB expression in ventral hippocampus regulates behavior in the social defeat model of depression

Authors: *C. MANNING, S. COOPER, A. EAGLE, M. THIBAULT, P. GAJEWSKI, M. MAZEI-ROBISON, A. ROBISON;
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Abstract: The ventral hippocampus is implicated in stress responses and motivated behaviors, and thus is an attractive target for studying the mechanisms of susceptibility and antidepressant actions after chronic social defeat stress (CSDS). We are therefore examining the role of the transcription factor ΔFosB in the ventral hippocampus in mediating behavioral responses to social stress and antidepressant effects on these behaviors. Chronic fluoxetine (Prozac©) ameliorates the behavioral deficits seen in susceptible animals after CSDS, and we report here that chronic fluoxetine also significantly increased the number of FosB reactive cells in all subregions of the ventral hippocampus. Further, Western blot revealed that chronic fluoxetine induces both ΔFosB and full-length FosB isoforms in the hippocampus of both animals exposed to defeat and controls. In order to determine whether ventral hippocampus FosB proteins play a role in behavioral responses to stress, we used targeted AAV-mediated expression of ΔJunD, a dominant negative variant of the FosB binding partner, in ventral hippocampus. We observed that inhibition of FosB transcriptional activity decreased the social interaction time after a single submaximal defeat compared to controls, suggesting that inhibition of FosB makes animals susceptible to stress. Taken together, these data suggest that FosB in the ventral hippocampus is a powerful modulator of the depressive-like symptoms induced by CSDS. We are currently investigating sex differences in stress- and fluoxetine-dependent induction of FosB proteins as well as their role in projections from the ventral hippocampus to other limbic and cortical regions important for stress responses.

Disclosures: C. Manning: None. **S. Cooper:** None. **A. Eagle:** None. **M. Thibault:** None. **P. Gajewski:** None. **M. Mazei-Robison:** None. **A. Robison:** None.

Poster

773. Mood Disorders: Antidepressants I

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: NIMH RO1MH092306

NARSAD Young Investigator Award

Robin Chemers Fellowship

Title: Pharmacological potentiation of KCNQ channel currents in midbrain dopamine neurons functions as a mechanistically distinct antidepressant

Authors: *A. K. FRIEDMAN[1], B. JUAREZ[1], S. M. KU[1], H. ZHANG[1], J. J. WALSH[1], D. CHAUDHURY[1], D. M. DIETZ[1], M. RIBADERNEIRA[2], E. WONG[2], R. NEVE[3], M.-H. HAN[1,4]; [1]Ichan Sch. of Med. at Mount Sinai, New York, NY; [2]CNS Pain Innovative Med. Unit,, AstraZeneca, Wilmington, DE; [3]McGovern Inst. for Brain Research, MIT, Boston, MA; [4]Friedman Brain Inst., New York, NY

Abstract: Although major depressive disorder is the second leading cause of disability worldwide, with less than half of patients achieving remission, there continues to be limited mechanistic diversity among the available antidepressants. This makes it imperative to develop new therapeutics. In particular, novel strategies may arise from utilizing recent insights into the understanding of natural resilience to social stress. Specifically these findings have demonstrated the importance of maintaining healthy activity of the dopamine (DA) neurons of the ventral tegmental area (VTA) in regulating mood. Thus, we explored the VTA DA circuit for novel therapeutic targets. Utilizing the well-established preclinical model of depression known as the chronic social defeat stress paradigm we demonstrated that resilient animals homeostatically maintain healthy DA neuron activity through a compensatory upregulation of potassium (K+) channels. To identify the K+ channel subunits necessary for this self-tuning plasticity we infused a selective inhibitor of KCNQ channels, XE-991, into the VTA of resilient mice. The inhibition of the KCNQ channels revealed the underlying stress-induced VTA hyperactivity and social avoidance. To determine if upregulation of this current is sufficient to behaviorally convert previously social avoidant and anhedonic mice we specifically expressed KCNQ3 in VTA dopamine neurons by injecting a Cre-inducible HSV-LS1L-KCNQ3-eYFP into the VTA of TH-Cre susceptible mice. The viral overexpression of KCNQ3 reversed both the stress induced hyperactivity and the susceptible phenotype. Specifically, expressing the KCNQ3 channel exclusively in the VTA to nucleus accumbens pathway reversed the social avoidance behavior. Together, this work indicated that the M-currents mediated by KCNQ channels as a valid therapeutic target for treating stress-induced depressive behavior. Therefore, we utilized currently available pharmacological K+ channel openers, flupirtine, BMS-204352 and retigabine and tested for antidepressant actions. Following a single infusion to the VTA of susceptible mice, there was a reversal of social avoidance and anhedonia indicating an antidepressant effect. Towards our translational goal, we found that repeated intraperitoneal injection of FDA-approved drug retigabine (ezogabine) also showed a consistent antidepressant effect. These

findings demonstrate that in naturally resilient mice KCNQ channel currents counteract the pathophysiological hyperactivity of VTA DA neurons and pharmacological potentiation of this process may function as a mechanistically unique antidepressant.

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Poster

773. Mood Disorders: Antidepressants I

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 773.29/G3

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: "Anna Licia Giovanetti" Award from University of Pavia, Italy

Title: Bioenergetics of Desipramine: a functional proteomic study

Authors: *F. FERRARI, A. GORINI, R. F. VILLA;
Dept. of Biol. and Biotech., Univ. of Pavia, Pavia, Italy

Abstract: BACKGROUND - Brain energy metabolism abnormalities in mood disorders were shown in neuroimaging studies on humans, indicating the normalization of tissutal bioenergetics after antidepressants (ADs) treatment [1]. In some experimental studies, ADs are inhibitors of mitochondrial function, while others indicate positive effects on mitochondrial energy metabolism. These conflicting results are due to the fact that the macro-heterogeneity of brain areas and ADs differential effects on pre-synaptic and on post-synaptic terminals have not been considered before. METHODS - The effects of 21-day treatment with the tricyclic antidepressant Desipramine (15 mg/kg, i.p.) were evaluated on energy metabolism of rat frontal cerebral cortex. Two populations of intra-synaptic mitochondria ("light" - LM; "heavy" - HM) were isolated according to Villa et al. [2] and the following enzyme activities have been assayed: citrate synthase (CS), succinate dehydrogenase (SDH), malate dehydrogenase (MDH) for Krebs' cycle; NADH-cytochrome c reductase (CCR), cytochrome oxidase (COX) for Electron Transport Chain; glutamate-oxaloacetate transaminase (GOT), glutamate-pyruvate transaminase (GPT) for glutamate and related amino acids metabolism. RESULTS - In controls, energy-linked enzyme activities are differently expressed in LM and HM, whose metabolic individuality is reflected by enzyme kinetics, as previously shown in physiological aging, experimental physiopathology and pharmacological treatments [3, 4]. In fact, in controls, SDH, COX, GOT and GPT activities were

higher in LM. Desipramine treatment decreased MDH, SDH and GPT activities in LM, while it enhanced CS and COX activities in HM. CONCLUSIONS - Desipramine modified the catalytic properties of energy-linked enzymes differentially respect to the types of intra-synaptic mitochondria, explaining at subcellular level and on functional proteomic basis the previously observed conflicting results about ADs on mitochondria. In this research, Desipramine exerted on the energy metabolism distinctive effects on pre-synaptic terminals and present data allow to integrate from a bioenergetic point of view the pharmacodynamic features of this paradigmatic drug. The study proceeds evaluating the effects of Fluoxetine on functional proteomics. REFERENCES - [1] Moretti et al 2003. Mol Psychiatry, 8:773-85; [2] Villa et al 1989. Cell Mol Neurobiol, 9:247-62; [3] Villa et al 2012. Neuroscience, 227:55-66; [4] Villa et al. 2013. Neurochem Int, 63:765-81. AKNOWLEDGEMENT - Dr. Ferrari was supported by “Anna Licia Giovanetti” Award from University of Pavia, Italy.

Disclosures: **F. Ferrari:** None. **A. Gorini:** None. **R.F. Villa:** None.

Poster

773. Mood Disorders: Antidepressants I

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 773.30/G4

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: R01 MH103322 from NIMH

Title: Potential antidepressant effects of kappa opioid receptor agonists following social defeat stress

Authors: ***A. LAMAN-MAHARG**, M. Z. MCMACKIN, E. O. SANCHEZ, K. L. CAMPI, B. C. TRAINOR;
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Abstract: Psychosocial stress leads to activation of kappa opioid receptors (KOR) which in turn facilitate depressive-like behaviors. This has generated a strong interest in the development of KOR antagonists as a potential novel class of antidepressant. However, most studies showing stress-induced activation of KOR focus on more short-term effects of stress and only study males. New evidence suggests that long-term effects of stress (over weeks or months) have important implications for KOR function, and that there may be sex differences. We examined the effects of social defeat stress on KOR action using California mice (Peromyscus californicus), a monogamous species in which social defeat can be studied in both males and

females. Behavioral observations were conducted two weeks after three episodes of social defeat or control conditions. A 10 mg/kg i.p. injection of KOR agonist U50,488 reduced social interaction behavior in females naïve to defeat. However, in stressed females U50,488 exerted an antidepressant effect, increasing social interaction to the level of controls treated with vehicle. In males there was a trend for U50,488 to reduce social interaction behavior in stressed males, suggesting a sex specific impact of social defeat. In addition, control females formed a conditioned place aversion to 2.5 mg/kg U50,448 and this aversion was blocked by stress. These results indicate that defeat stress may induce long-term changes in KOR activation in females. Ongoing studies are investigating additional measures of depressive-like behaviors and potential mechanisms underlying this effect. These data suggest that KOR agonists could potentially have novel antidepressant effects in the context of stress-induced psychiatric disorders.

Disclosures: A. Laman-Maharg: None. **M.Z. McMackin:** None. **E.O. Sanchez:** None. **K.L. Campi:** None. **B.C. Trainor:** None.

Poster

774. Mood Disorders: Antidepressants II

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 774.01/G5

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Further characterization of the discriminative stimulus properties of the noncompetitive N-Methyl-D-aspartate (NMDA) receptor antagonist ketamine in rats

Authors: C. M. MERRITT[1], A. M. JONES[1], J. C. CORNELISSEN[1], B. L. JOSEPH[1], K. A. WEBSTER[1], T. M. HILLHOUSE[2], *J. H. PORTER[1];
[1]Psychology, Virginia Commonwealth Univ., Richmond, VA; [2]Pharmacol., Univ. of Michigan, Ann Arbor, MI

Abstract: Findings that the noncompetitive N-Methyl-D-aspartate (NMDA) receptor antagonist ketamine produces rapid and sustained antidepressant effects in patients with major depressive disorder has engendered a great deal of interest in glutamatergic targets for the treatment of depression. However, the abuse liability of ketamine remains a concern. The subjective effects of drugs, which may be associated with both abuse-related and therapeutic effects, can be assessed with the drug discrimination paradigm. Drug discrimination procedures also provide information about the underlying receptor mechanisms that mediate a drug's subjective effects (i.e. its discriminative stimulus properties). We previously reported that ketamine's discriminative stimulus properties appear to be mediated only by antagonism of NMDA receptors as only the

noncompetitive NMDA antagonists MK-801 and memantine fully substituted for ketamine. The present study was designed to further characterize ketamine's discriminative stimulus properties with selective ligands tested alone and in combination with ketamine in Sprague-Dawley rats trained to discriminate 10.0 mg/kg ketamine from saline is a two-lever drug discrimination procedure for food reinforcement. As expected, the noncompetitive NMDA antagonist phencyclidine (1.78 mg/kg) fully substituted for ketamine. In contrast, substitution testing with the selective ligands raclopride (dopamine D2/D3 antagonist), quinpirole (D2/D3 agonist), U69593 (opioid kappa agonist), scopolamine (cholinergic muscarinic antagonist), oxotremorine (muscarinic agonist), yohimbine (alpha 2 adrenoceptor antagonist), pyrilamine (histamine H1 antagonist), ritanserin (serotonin 5-HT2 antagonist), and naloxone (opioid mu antagonist) failed to reveal any ketamine-appropriate responding. Interestingly, when tested in combination with a low, non-discriminated dose (2.5 mg/kg) of ketamine, both raclopride (D2 antagonist, 0.18 mg/kg dose) and quinpirole (D2/D3 agonist, 0.056 mg/kg dose) produced a significant increase in ketamine-appropriate responding (57% drug lever responding and 61% drug lever responding, respectively). While ketamine's discriminative stimulus properties are primarily mediated by antagonism of NMDA receptors, these results reveal that the dopamine system may interact with ketamine's discriminative stimulus properties.

Disclosures: C.M. Merritt: None. **A.M. Jones:** None. **J.C. Cornelissen:** None. **B.L. Joseph:** None. **K.A. Webster:** None. **T.M. Hillhouse:** None. **J.H. Porter:** None.

Poster

774. Mood Disorders: Antidepressants II

Location: Hall A

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Program#/Poster#: 774.02/G6

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: NIMH Grant R01MH079103

Title: A novel class of fast-acting antidepressants: converging evidence using genetic knockdown and two mechanistically distinct GLO1 inhibitors

Authors: *K. M. MCMURRAY[1], P. S. SIDHU[3], P. ELKIN[2], V. RAWAL[2], L. A. ARNOLD[3], A. A. PALMER[1];
[1]Human Genet., [2]Univ. of Chicago, Chicago, IL; [3]Univ. of Wisconsin-Milwaukee, Milwaukee, WI

Abstract: Major depressive disorder (MDD) is a highly prevalent and debilitating psychiatric disorder. Despite a variety of available treatments for MDD, positive patient outcomes are limited due to a slow onset of therapeutic effects (2-4 weeks), adverse side effects (weight gain, insomnia) or a lack of response to treatment in a large portion of patients (~50%). Thus, identifying novel systems and molecular targets for treatment is of paramount importance. We recently identified Glyoxalase I (GLO1) as a novel target for the treatment of depression. GLO1 is a ubiquitous cellular enzyme responsible for the detoxification of methylglyoxal (MG), which is a byproduct of glycolysis. We previously showed that MG is a competitive partial agonist at GABA-A receptors and that inhibition of GLO1 increases MG concentrations within the brain and reduces anxiety-like behaviors in mice. While GABA-A receptor agonists are not typically used to treat depression, associations between Glo1/MG and depression-like behavior were previously seen in mice. Thus, we investigated the effects of GLO1 inhibition on depression-like behavior in mice using both genetic knockdown and two mechanistically distinct small molecule GLO1 inhibitors. The tail suspension test (TST) and forced swim test (FST) are assays of antidepressant efficacy. Mice treated acutely with antidepressants spend more time performing escape-oriented behaviors than immobile postures relative to no treatment. We found that both genetic and pharmacological inhibition of GLO1 by two mechanistically distinct inhibitors reduced immobility in the TST and FST without affecting locomotor behavior in the open field test. The chronic FST and olfactory bulbectomy (OBX) models selectively respond to chronic treatments (14 day) with classical antidepressants (Fluoxetine; SSRI) mimicking the clinical time-course of antidepressant action in humans. Mice were tested in both chronic FST and OBX to establish a time-course of therapeutic onset. We found that pharmacological inhibition of GLO1 reduced depression-like behavior in models sensitive to chronic treatment with classical antidepressants to a similar extent as fluoxetine by 14 days of treatment. Further, pBBG reduced depression-like behavior in these models and upregulated proteins associated with antidepressant onset (BDNF, pCREB/CREB) by 5 days of treatment suggesting that GLO1 inhibitors may be novel fast-acting antidepressants.

Disclosures: K.M. McMurray: None. **P.S. Sidhu:** None. **P. Elkin:** None. **V. Rawal:** None. **L.A. Arnold:** None. **A.A. Palmer:** None.

Poster

774. Mood Disorders: Antidepressants II

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 774.03/G7

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: KU Institute of Reproductive Health and Regenerative Medicine

KU new faculty research fund and start-up fund

Title: Estrogen receptor β regulation of bdnf-5-ht dual signaling: mechanistic and therapeutic implications for menopausal depression

Authors: *A. CHHIBBER, S. K. WOODY, L. ZHAO;
Univ. of Kansas, Lawrence, KS

Abstract: Depression is likely not a single disorder but a heterogeneous syndrome comprised of multiple pathological phenotypes of distinct causes. Depression currently affects 350 million people worldwide and 19 million Americans each year. Women are 70% more likely to develop depression than men, and susceptibility to depression is highest during the endocrine transition from premenopause to postmenopause. Estrogen receptor β (ERβ) has been indicated to be involved in the pathophysiology of mood disorders; however, the underlying mechanisms are poorly understood. In this study, we sought to investigate the role of ERβ in the regulation of brain-derived neurotrophic factor (BDNF) and serotonin (5-HT) signaling that have been hypothesized as two major and interrelated pathways associated with depression. Our analyses in ERα and ERβ knockout mouse (ERα-/- and ERβ-/-) models demonstrated that BDNF was significantly down regulated in ERβ-/- but not ERα-/- mice, and ERβ-/--mediated response was brain region-specific. A nearly 50% reduction in BDNF level was found in the hippocampus of ERβ-/- mice; in contrast, the changes in BDNF were at a much smaller magnitude and insignificant in the cortex and hypothalamus of these mice. These data were further validated in two ERβ-/- rat models, one with targeted deletion of exon 3 and the other with deletion of exon 4 in the ERβ gene. We found that ERβ deficiency in both models resulted in a significantly reduced level of both BDNF and its receptor, tyrosine kinase B (TrkB), in the hippocampus of ERβ-/- rats. Our further analyses in primary hippocampal neurons indicated that activation of ERβ significantly enhanced BDNF-TrkB signaling and the downstream cascades involved in neurogenesis and synaptic plasticity. Clinical studies have shown that depression decrease BDNF levels in the hippocampus which can be reversed back to the normal levels after the antidepressant treatment. Thus, our findings suggest that ERβ signaling perturbation and the resultant decreased BDNF-TrkB signaling could play a role in the increased susceptibility for depression associated with menopause. In addition to BDNF signaling, our study also addresses the deficits in postsynaptic 5-HT signaling associated with ERβ signaling deficiency in the hippocampus, which adds additional insights into our understanding of the mechanisms by which ERβ could play an essential role in both the development and intervention of depressive disorders in perimenopausal and menopausal women.

Disclosures: A. Chhibber: None. **S.K. Woody:** None. **L. Zhao:** None.

Poster

774. Mood Disorders: Antidepressants II

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Behavioral effects of single dose ketamine injection on adult rats exposed to chronic unpredictable mild stress

Authors: *E. ULUPINAR[1], E. POLAT[2], O. O. AYDIN[2], E. G. AYDIN[3];
[2]Neurosci., [3]Pharmacol., [1]Eskisehir Osmangazi Univ., Eskisehir, Turkey

Abstract: NMDA receptor antagonist ketamine has been associated with rapid and effective anti-depressant effects in patients with treatment-resistant major depression. Effects of a single dose of ketamine may start within hours and sustain for up to 2 weeks. Chronic unpredictable stress is an animal model mimicking the stressful events that may precipitate clinical depression in humans. In this study, we investigated the behavioral effects of single ketamine injection in chronically stressed animals. Adult male Sprague-Dawley rats (n=12) were subjected daily to a random pattern of unpredictable mild stressors for 28 days. Control rats were handled daily during the same period. After the final stressor, half of the rats from each treatment and control group received an intraperitoneal injection of ketamine (10 mg/kg), while others receiving equal volume of saline injections. Next day, rats were tested for behavioral effects in the forced swim, sucrose preference, open field and suspension tests. Following intracardiac perfusion, body, brain and adrenal weights were measured. Animals subjected to stress had significantly higher adrenal to body weight ratios, and displayed decreased immobility in the forced swim test suggesting that the stress paradigm induced higher levels of blood corticosterone and a depression-like phenotype. However, ketamine injection did not alter the immobility time of stressed animals in the forced swim test. No difference was observed in the open field test and sucrose consumption of animals was also similar following ketamine injections. Suspension test scores of stressed animals were worse than controls, but ketamine improved the test performances of animals. Our results suggest that the depressive-like behavior induced by chronic unpredictable mild stress was not completely reverted by single dose ketamine injection. These observations are not consistent with previous reports that sub-anesthetic doses of ketamine have acute and potent antidepressant effects in humans and animal models. Therefore, further studies needs to be done to reveal antidepressant efficacy of ketamine not only at behavioral level, but also at morphological and molecular level.

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Poster

774. Mood Disorders: Antidepressants II

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 774.05/G9

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Characterization of the discriminative stimulus properties noncompetitive N-Methyl-D-aspartate (NMDA) receptor antagonist ketamine in C57BL/6 mice

Authors: *R. PANDEY, C. W. KALINOWSKI, K. W. LOVELESS, K. A. WEBSTER, J. H. PORTER;
Psychology, Virginia Commonwealth Univ., Richmond, VA

Abstract: Ketamine is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist with dissociative anesthetic properties, and it has long been considered a club drug as certain countries continue to have problems with a high level of ketamine abuse. Despite its abuse profile ketamine has been shown to produce both rapid and long-lasting antidepressant effects in patients with major depressive disorder, especially treatment-resistant patients; however, its abuse liability limits its outpatient use. Identifying the receptor mechanisms associated with ketamine could help lead to drug development of a novel treatment for depression. The present study investigated the interoceptive effects of ketamine as a discriminative cue in a standard two lever drug discrimination study for food reinforcement. Male C57BL/6 mice were trained to discriminate 10 mg/kg of ketamine from vehicle in a two-lever drug discrimination task (10 min injection time, sc). Mice quickly acquired ketamine's discriminative cue (mean = 19.6 days, SEM = 1.21, range 8-29). Then, a ketamine generalization curve (2.5 mg/kg - 20.0 mg/kg) was conducted and yielded an ED50 = 4.38 mg/kg (95% = CI 4.03 mg/kg-4.76 mg/kg). A time course was conducted (0-100 minutes) to examine the behavioral pharmacokinetic effects of ketamine and revealed that ketamine was rapidly absorbed producing full generalization at the 0 and 10 minute injection times, but was eliminated quickly as only vehicle-appropriate responding was evident by 30 minutes. Substitution testing with the NMDA receptor antagonists, phencyclidine (PCP), memantine, and MK-801 produced full substitution for ketamine's discriminative stimulus. PCP fully substituted at 3.2 mg/kg, yielding an ED50 = 1.23 mg/kg (95% CI = 1.00 mg/kg - 1.53 mg/kg), producing significant rate suppression. MK-801substituted at 0.1 and 0.18 mg/kg, yielding an ED50 = 0.08 mg/kg (95% CI 0.07mg/kg - 0.09mg/kg) with no reduction in response rates. Memantine substituted at 20.0 mg/kg, yielding an ED50 = 9.17 mg/kg (95% CI = 7.23 mg/kg - 11.64 mg/kg), producing significant rate suppression. We also tested the selective serotonin reuptake inhibitor antidepressant fluoxetine (2.5 - 20 mg/kg) and

the tricyclic antidepressant imipramine (1.0 - 17.8 mg/kg). Both drugs failed to substitute for ketamine at any of the doses tested. This study replicates previous findings in ketamine discrimination with rats, demonstrating that ketamine's discriminative stimulus properties are primarily mediated by antagonism at glutamatergic NMDA receptors. Finally, ketamine's interoceptive effects appear to be independent of its antidepressant-like properties.

Disclosures: R. Pandey: None. **C.W. Kalinowski:** None. **K.W. Loveless:** None. **K.A. Webster:** None. **J.H. Porter:** None.

Poster

774. Mood Disorders: Antidepressants II

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: an Alzheimer's Association Investigator Initiated Research Grant (133086)

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a UMMC MIND center subcontract

Title: Impact of alternative RNA splicing of ERβ on ovarian hormone deficiency-induced depression and estrogen therapy effectiveness in female rats

Authors: *X. HOU[1], S. O. ADEOSUN[2], R. HILL[2], B. ZHENG[2], J. WANG[2,3,4,1];
[1]Program in Neurosci., [2]Dept. of Pathology, [3]Dept. of Psychiatry and Human Behavior, [4]Dept. of Pharmacol. and Toxicology, Univ. of Mississippi Med. Ctr., Jackson, MS

Abstract: Depression is a serious psychiatric condition that interferes with patients' daily life. Women are more susceptible to depressive disorders than men, with a particularly high risk during hormone fluctuations especially at menopause. Estrogen therapy (ET), an effective treatment for perimenopausal depression, often fails to ameliorate symptoms when initiated late after the onset of menopause. Our previous work suggested that the differential effects of ET might be mediated via the alternative RNA splicing of estrogen receptor (ER) β. To further understand the mechanism, we used a customized RT2 Profiler PCR Array to examine expressions of 84 RNA splicing factors in the frontal cortex from female rats receiving E2 or

vehicle 6- (early) or 180- (late) day after ovariectomy (OVX). To study the ER isoform specific effects in the late treatment, two additional 180-day OVX rat cohorts received ERβ or ERα selective agonists. Results showed that OVX increased (SFRS7 and SFRS16) or decreased (ZRSR2 and CTNNB1) mRNA levels of splicing factors in the frontal cortex, while early E2 treatment largely reversed these. Early E2 also decreased ERβ2 expression in leukocytes, increased rat swimming time in the forced swim test and increased TPH2 RNA and protein expression in the dorsal raphe. DPN, an ERβ selective agonist, but not E2 or PPT, and ERα selective agonist, achieved similar results in the late treatment. These data support that the effectiveness of ET is mediated by alternative splicing of ERβ, and ERβ specific ligands may serve as an effective treatment late after the onset of menopause.

Disclosures: X. Hou: None. **S.O. Adeosun:** None. **R. Hill:** None. **B. Zheng:** None. **J. Wang:** None.

Poster

774. Mood Disorders: Antidepressants II

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 774.07/G11

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: The effect of allopregnanolone infusion on GABAa receptor subunits mRNA expression in the prefrontal cortex of rats

Authors: *M. S. NIN[1], F. B. ALMEIDA[2], G. AGNES[3], H. M. T. BARROS[2];
[2]Pharmacolgy, [3]Mol. Biol., [1]UFCSPA, Porto Alegre, Brazil

Abstract: Allopregnanolone is a neurosteroid capable of producing an antideprssant-like effect in rats. It is believed that this effect is due to its interaction with the GABAA receptors (GABAA-R), in which allopregnanolone plays a role as a positive modulator. However, allopregnanolone influence on GABAA-R subunits mRNA expression in specific brain regions is still not completely elucidated, as well as its asymmetrical role. In this work, we evaluated the effect of bilateral infusion of three doses of allopregnanolone (low: 1.25 μg/rat; intermediate: 2.5 μg/rat; and high: 5 μg/rat) in the prefrontal cortex of Wistar male rats on the mRNA expression of GABAA-R subunits γ2 and δ in both hemispheres of the same region infused using the realtime quantitative PCR technique (endogenous control genes: β-actin and GAPDH). As results, there was no difference between hemispheres on the δ subunit mRNA expression ($P = 0.971$), but the high dose of allopregnananolone was able to increase its mRNA expression when compared to controls ($P = 0.001$) and the low dose ($P = 0.004$). In the γ2 subunit, the right

hemisphere had a higher mRNA expression than the left hemisphere in the controls (P = 0.007) and in the low dose (P = 0.011). The γ2 mRNA expression was increased only in the left hemisphere by the high dose when compared to controls (P = 0.013) and the low dose (P = 0.007), while in the right hemisphere there was no significant change. These results indicate that allopregnanolone is capable of increasing the mRNA expression of δ and γ2, the latter being specifically on the left hemisphere, normalizing an asymmetry found in animals with no treatment.

Disclosures: **M.S. Nin:** None. **F.B. Almeida:** None. **G. Agnes:** None. **H.M.T. Barros:** None.

Poster

774. Mood Disorders: Antidepressants II

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 774.08/G12

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Treatment with high-voltage electric potential (HELP) induces tolerance to psychosomatic stress and increases cortical BDNF levels

Authors: *K. YAMATO[1], T. HORI[1,3], Y. NAKAJO[1,4], H. KATAOKA[2], J. C. TAKAHASHI[2], H. YANAMOTO[1,5];
[1]Lab. of Neurol. and Neurosurg., [2]Dept. of Neurosurg., Natl. Cerebral and Cardiovasc. Ctr., Suita, Japan; [3]Hakuju Inst. for Hlth. Sci. Co. Ltd., Tokyo, Japan; [4]Res. Laboratory, Rakuwa-kai Otowa Hosp., Kyoto, Japan; [5]Dept. of Cardiovasc. Science, Div. of Surgical Med., Osaka Univ. Grad. Sch. of Med., Suita, Japan

Abstract: Development of depressive disorders is common throughout life. Decreased intracerebral brain-derived neurotrophic factor (BDNF) level has been identified as an etiologic factor in the pathogenesis of depression. Recently, we found that repetitive treatment with high-voltage electric potential (HELP) increases brain BDNF levels, enhances learning and memory, and affords tolerance to infarct lesion development in mice. However, direct evidence showing that HELP-induced increase in BDNF levels results in improved tolerance to development of depressive symptoms is lacking. In the present study, we investigated the effect of HELP on the development of a depressive symptom by subjecting mice to an unpleasant psychosomatic stress (swimming). C57BL/6J mice were exposed to 6.0 (17.3 kV/m), 7.8 (22.5 kV/m), or 9.0 kV (26.0 kV/m) HELP at 60 Hz for 5 hours per day for 21 consecutive days. After this treatment, the total climbing time (time spent in trying to escape from the water) after training on a forced swim stress was measured. In addition, regional BDNF levels in the brain were measured before and

after stress exposure. The climbing time was significantly increased in the treatment group compared with the control group (P<0.05, Bonferroni correction). HELP treatment increased BDNF levels in the cortex. BDNF levels in the cortex, but not in the caudate putamen and hippocampus, correlated with induction of tolerance. Repetitive exposure to HELP induces tolerance against development of depressive symptoms, accompanied by increases in cortical BDNF levels. Thus, repeated HELP treatment has an antidepressant effect.

Disclosures: K. Yamato: None. **T. Hori:** None. **Y. Nakajo:** None. **H. Kataoka:** None. **J.C. Takahashi:** None. **H. Yanamoto:** None.

Poster

774. Mood Disorders: Antidepressants II

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: PhD studentship from Government of Saudi Arabia (AA)

Title: The antidepressant-like effects of BU10119, a novel kappa opioid receptor antagonist, in the novelty-induced hypophagia task in mice

Authors: *S. J. BAILEY[1], A. ALMATROUDI[1], C. P. BAILEY[2], S. M. HUSBANDS[2]; [2]Pharm. & Pharmacol., [1]Univ. of Bath, Bath, United Kingdom

Abstract: Antagonists at kappa-opioid receptors have been proposed as novel antidepressants. The standard high-affinity, selective kappa-antagonists have a long lasting duration of action which potentially limits their use (Carroll and Carlezon 2013. J Med Chem 56: 2178-2195). We have previously shown that the combination of buprenorphine (1mg/kg) with naltrexone (1mg/kg) produced a functional short-acting kappa-antagonist, that was non-sedating and non-rewarding, with antidepressant like effects in the forced swim test and novelty-induced hypophagia task (Almatroudi et al. 2015. J. Psychopharmacol. In Press). We have developed a novel compound that combines the properties of buprenorphine/naltrexone combination into a single compound (Cueva et al. 2015. J Med Chem, In Press), thereby simplifying dosing and treatment regimens and avoiding abuse potential. Here, we present preliminary data that BU10119 is a functional kappa antagonist with antidepressant-like effects in mice. Adult male CD-1 mice (8-9 weeks) were used. For novelty-induced hypophagia, mice were individually housed and trained for 3 days to consume condensed milk. On test days, mice were injected intraperitoneally (10 ml/kg) with saline, buprenorphine/naltrexone combination (1 mg/kg),

fluoxetine (20 mg/kg) or BU10119 (1mg/kg) one hour prior to testing behaviour. The latency to drink and consumption were recorded in the home cage (day 4) and in the novel cage (day5). One-way ANOVA, revealed that there was a significant effect of drug treatment on the latency to drink in the novel cage ($F(4, 45) = 9.15$, $P<0.001$) but not consumption ($F(4, 45) = 1.25$, $P=0.3$). BU10119 is a relatively short acting kappa-antagonist with little efficacy at the mu-opioid receptor. BU10119 has demonstrated activity in the novelty-induced hypophagia test that is consistent with the behavioural effects of fluoxetine and therefore has an antidepressant-like profile.

Disclosures: S.J. Bailey: None. **A. Almatroudi:** None. **C.P. Bailey:** None. **S.M. Husbands:** None.

Poster

774. Mood Disorders: Antidepressants II

Location: Hall A

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Program#/Poster#: 774.10/G14

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: FDT20140930830

Title: Striatopallidal Gpr88 regulates anxiety-like behaviour and dopaminergic driven locomotion

Authors: *A. MEIRSMAN[1], J. BECKER[2], B. KIEFFER[3];
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Abstract: GPR88 is a brain orphan G protein coupled receptors, highly and mainly expressed in the striatum, specifically in medium spiny neurons (MSNs) of both the striatonigral (co-expressing dopamine D1 receptors_D1R and Substance P) and striatopallidal (co-expressing dopamine D2 receptors_D2R and adenosine A2A receptor_A2AR) pathway (Massart, Eur J Neurosci 2009). Previous reports (Logue, Mol Cell Neurosci; Quintana, Nature Neurosci 2012) show that Gpr88 Knockout (KO) mice display behavioral deficits evocative of striatal dysfunction, and our recent work also demonstrates emotional deficits (Meirsman in revision). However, no study to date has addressed the specific function of Gpr88 in each of the two main MSNs subpopulations. To elucidate GPR88 function in striatopallidal MSNs we induced the Gpr88 gene knockout exclusively in these neurons and assessed behavioral performance of

conditional KO mice (cKO). The cKO of Gpr88 in striatopallidal MSNs was obtained by crossing Gpr88-floxed mice with A2A-Cre mice (Durieux, Nature Neurosci 2009). Cell-specific deletion was verified using fluorescent *in situ* hybridization with D1R, D2R and Gpr88 probes. We then evaluated motor functions (e.g., locomotor activity in the open Field, rotarod), locomotor responses to dopaminergic agonists (SKF and Quinpirole) and anxiety-like behaviors (e.g., elevated-Plus Maze, Light-Dark) in conditional A2A-Gpr88 mice. Results indicate that, as for total Gpr88 knockout mice, A2A-Gpr88 mice show hyperactive behaviour in a novel environment and decreased anxiety-like behavior. In contrast to the total null mutant, however, A2A-Gpr88 mice show no motor coordination deficit, and also show increased and decreased D1R (SKF) and D2R (Quinpirole) agonist-induced locomotor response, respectively. We conclude that Gpr88 in the striatopallidal pathway regulates locomotion and exploratory behaviour, possibly by regulating D1R and D2R dopaminergic transmission, and also modulate anxiety-like behavior by mechanisms that remain to be determined.

Disclosures: **A. Meirsman:** None. **J. Becker:** None. **B. Kieffer:** None.

Poster

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: Swiss National Science Foundation Grant 31003A-135692

National Center for Competence in Research (NCCR) Synapsy

Title: Involvement of the agmatinergic system in the depressive-like phenotype of the CREB-regulated transcription coactivator 1 knockout mouse model of depression

Authors: *E. M. MEYLAN[1,2], L. BREUILLAUD[1,2], T. SEREDENINA[3], P. J. MAGISTRETTI[3,1,4], O. HALFON[2], R. LUTHI-CARTER[3,5], J.-R. CARDINAUX[1,2];
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Abstract: Recent studies have highlighted the involvement of the arginine-decarboxylation product agmatine in depression. Most notably, it has been shown that this compound has

antidepressant properties in rodents and that agmatinase (Agmat), the agmatine-degrading enzyme, is upregulated in the brains of mood disorders patients. We have previously shown that mice lacking CREB-regulated transcription coactivator 1 (CRTC1) associate behavioral and molecular depressive-like endophenotypes, as well as blunted responses to classical antidepressants. Here, the molecular basis of the behavioral phenotype of Crtc1 knockout (KO) mice was further examined using microarray gene expression profiling. This analysis revealed an upregulation of Agmat in the cortex of Crtc1 KO mice. Quantitative polymerase chain reaction and Western blot analyses confirmed Agmat upregulation in Crtc1 KO mice prefrontal cortex and hippocampus. Immunohistochemical data showed that Crtc1 KO mice display more agmatinase-expressing cells than wild-type mice in several brain regions, including the prefrontal cortex and the CA1, CA3 and dentate gyrus regions of the hippocampus. We also observed that agmatinase was most notably expressed in parvalbumin and somatostatin interneurons. At the behavioural level, acute agmatine treatment rapidly (30 min) improved the depressive-like behavior of Crtc1 KO mice in the forced swim test, suggesting that exogenous agmatine has a rapid antidepressant effect through the compensation of agmatine deficit due to upregulated Agmat. In wild type mice PFC, agmatine rapidly increased Brain-derived neurotrophic factor (BDNF) protein levels and decreased eukaryotic elongation factor 2 (eEF2) phosphorylation, indicating that agmatine might be a fast-acting antidepressant with NMDA receptor antagonist properties. Collectively, these findings implicate Agmat in the depressive-like phenotype of Crtc1 KO mice, refine current understanding of the agmatinergic system in the brain and highlight its putative role in major depression.

Disclosures: E.M. Meylan: None. **L. Breuillaud:** None. **T. Seredenina:** None. **P.J. Magistretti:** None. **O. Halfon:** None. **R. Luthi-Carter:** None. **J. Cardinaux:** None.

Poster

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Support: MIUR Prin 2008, 200894SYW2

Toscana Life Sciences Foundation Orphan_0108 program

Title: Depression-like behavior and response to chronic stress in mice lacking brain serotonin

Authors: *G. MADDALONI[1], S. MIGLIARINI[1], F. NAPOLITANO[2], A. USIELLO[2], M. PASQUALETTI[1,3];
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Abstract: During their lives, virtually all living organisms have to face disturbing forces that upset their homeostasis. These forces, called stressors, trigger a stress response, an innate adaptive response whose task is restoring normal balance of the organism, essential for survival. In vertebrates the brain is central in the adaptation to stress, both in the perception of the stressors and in the organization of the stress response. However, due to a combination of genetic factors and environmental agents, not always a stress response is able to face the stressors, and a maladaptive stress response further destabilizes animal homeostasis, generating stress-related neuropsychiatric disorders such as depression and anxiety. Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter that has a central role in normal brain function modulating several physiological processes including mood regulation and emotional behavior, and it has been implicated both in an adaptive and maladaptive stress response. Indeed, several polymorphisms identified in genes involved in serotonin signaling are associated with neuropsychiatric diseases such as depression and anxiety. Moreover, according to the monoamine hypothesis of depression, a reduction of serotonin signaling could be one of the major causes. Current antidepressants act on serotonergic signaling, elevating 5-HT concentration in the synaptic cleft, and showing therapeutic effects 2 to 4 weeks after administration, with a considerable number of patients resistant to the treatment. Therefore, the precise role of serotonin in the modulation of emotional behavior in health and disease needs to be further elucidated. We used a Tph2 knock-out mouse model to evaluate the consequences of brain serotonin depletion on the emotional behavior testing adult animals for behavioral despair. Tph2 mutant mice displayed reduced depression-like behaviors in the forced swim test, in the tail suspension test, as well as in the novelty food suppressed test. We then asked how exposure to Unpredictable Chronic Mild Stress (UCMS), an effective paradigm for inducing depression-like symptoms in rodents, could influence the behavior of animals lacking brain serotonin. Results showed that UCMS induces depressive-like behavior in the forced swim test in both Tph2 -/- and control littermates with a greater increase in immobility between non-stressed and stressed mutant mice than between non-stressed and stressed wt animals. Finally, we are currently treating stressed Tph2 -/- mice with ketamine, a NMDA-R antagonist with rapid and effective antidepressant action, in order to asses if 5-HT is required for its therapeutic effect.

Disclosures: G. Maddaloni: None. **S. Migliarini:** None. **F. Napolitano:** None. **A. Usiello:** None. **M. Pasqualetti:** None.

Poster

774. Mood Disorders: Antidepressants II

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Program#/Poster#: 774.13/G17

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: MRI and MRS characterization of Crtc1 knockout mice limbic structures: investigating neurobiology of mood disorders

Authors: *A. CHERIX[1,2], R. GRUETTER[3,4], H. LEI[6,5], J.-R. CARDINAUX[2,7];
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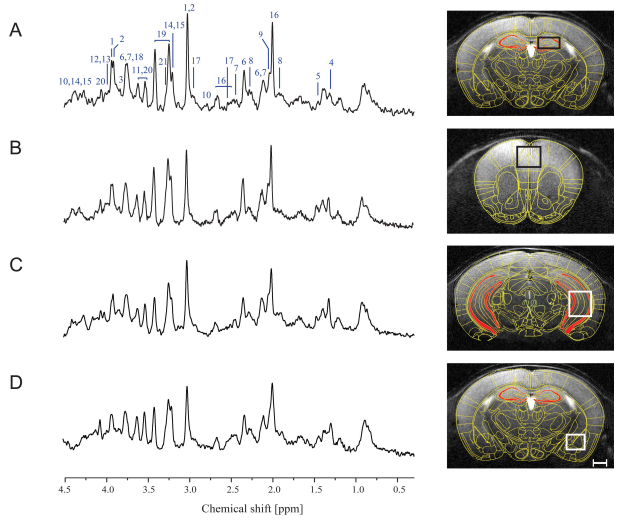
Abstract: *In vivo* magnetic resonance (MR) imaging (MRI) and spectroscopy (MRS) are two non-invasive techniques of choice for investigating and monitoring brain metabolic and structural changes in mood disorders, which are poorly understood. Discrepancies between human studies reflect however the lack of comprehension of their pathophysiology and reinforce the need for an endophenotypic characterization, which can be provided by animal models. We have investigated the metabolic and volumetric status of a previously reported mouse model of mood disorders lacking an important brain plasticity gene, Crtc1 (CREB-regulated transcriptional coactivator 1). Crtc1 knockout (KO) animals are considered as relevant for studying mood disorders, because they show neurobehavioral depressive-like endophenotypes, as well as late-onset obesity, together with monoaminergic system dysfunctions (Breuillaud, et al. Biol Psychiatry. 2012, 72(7):528-36 ; Breuillaud, et al. Nature Medicine. 2009, 15(9) :989 - 990). Metabolic and volumetric profile alterations were determined with T2-weighted MRI together with 1H-MRS of prefrontal cortex (PFC), dorsal/ventral hippocampus and amygdala. Crtc1 KO mice showed reduced glutamate (-12%, p=0.0056) and GABA (-26%, p=0.03) in PFC, whereas a marked reduction of the energy metabolite phosphocreatine (-20%, p=0.03) was visible in the dorsal hippocampus. KO mice also showed a strong ventricle shrinkage correlating (p=0.01) with swelling of surrounding gray matter. Such alterations are consistent with human MR findings in mood disorders (Sanacora, et al. Neuropharmacology. 2012, 62(1):63-77; Stork and Renshaw. Mol Psychiatry. 2005, 10(10):900-19), which suggested that the GABA/glutamatergic system or the energy metabolism are impaired in specific regions of the brain. This mouse model should thus allow a better understanding of the molecular mechanisms underlying the changes of MRI/MRS markers observed in human mood disorders.



Disclosures: **A. Cherix:** None. **R. Gruetter:** None. **H. Lei:** None. **J. Cardinaux:** None.

Poster

774. Mood Disorders: Antidepressants II

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: T32 DA031111

NIH MH082876

NIH DA023988

Title: Differential roles of homologous circadian proteins in plasticity and reward behavior

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Abstract: The circadian molecular clock regulates monoaminergic systems that control reward behaviors and are relevant to addiction. We investigated how disruptions in the homologous circadian transcription factors, CLOCK and NPAS2, lead to differential physiological alterations in mesolimbic circuitry and sensitivity to drugs of abuse. Using *Clock* mutant mice (*Clock*19), a model of bipolar mania, we measured excitatory synaptic strength of medium spiny neurons

(MSNs) in the nucleus accumbens (NAc), an area that receives a dense dopaminergic (DA) projection from the ventral tegmental area (VTA) and is critical for motivated behavior. *Clock* mutant mice display an increased preference for cocaine and abnormal VTA DA signaling which may affect plasticity in target regions. In addition to reduced levels of GluA1 protein and alterations in intrinsic membrane properties, they also have reduced AMPA-mediated synaptic strength of MSNs with no change in presynaptic release of glutamate indicating a postsynaptic adaptation. These changes represent potential compensatory mechanisms as a result of increased DA transmission. We also examined the effect of viral-mediated knock down (KD) of NPAS2 in C57BL/6J mice on the conditioned response to cocaine and synaptic strength of MSNs. Both a global *Npas2* mutation along with NAc-specific NPAS2 KD caused a decrease in cocaine preference and KD produced an increase in mEPSC amplitude in MSNs compared with scramble virus. The results of our study suggest an important role for circadian transcriptional mechanisms in the regulation of synaptic activity and reward-related behavior. They also highlight differential roles of two homologous circadian proteins in these important functions.

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Poster

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: Swiss National Science Foundation Grant 31003A-135692

National Centre of Competence in Research (NCCR) Synapsy

Title: The histone deacetylase inhibitor SAHA improves the depressive-like behavior of CREB-regulated transcription coactivator 1-deficient mice: possible relevance for treatment-resistant depression

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Abstract: Major depression is a highly complex disabling psychiatric disorder affecting millions of people worldwide. Despite the availability of several classes of antidepressants, a substantial percentage of patients are unresponsive to these medications. A better understanding of the neurobiology of depression and the mechanisms underlying antidepressant response is thus critically needed. We previously reported that mice lacking CREB-regulated transcription coactivator 1 (CRTC1) exhibit a depressive-like phenotype and a blunted antidepressant response to the selective serotonin reuptake inhibitor fluoxetine. In this study, we similarly show that Crtc1 knockout (ko) mice are resistant to the antidepressant effect of chronic desipramine in a behavioral despair paradigm. Supporting the blunted response to this tricyclic antidepressant, we found that desipramine does not significantly increase the expression of brain-derived neurotrophic factor (Bdnf) and orphan nuclear receptors (Nr4as) in the hippocampus and prefrontal cortex of Crtc1 ko mice as it does in wild-type animals. Epigenetic regulation of neuroplasticity gene expression has been associated with depression and antidepressant response, and histone deacetylase (HDAC) inhibitors have been shown to have antidepressant-like properties. Here, we show that unlike conventional antidepressants, chronic systemic administration of the HDAC inhibitor SAHA partially rescues the depressive-like behavior of Crtc1 ko mice. This behavioral effect is accompanied by an increased expression of Bdnf, but not Nr4as, in the prefrontal cortex of these mice, suggesting that this epigenetic intervention restores the expression of a subset of genes by acting downstream of CRTC1. These findings suggest that CRTC1 alterations may be associated with treatment-resistant depression, and support the interesting possibility that targeting HDACs may be a useful therapeutic strategy in antidepressant development.

Disclosures: J. Cardinaux: None. **E.M. Meylan:** None. **O. Halfon:** None. **P.J. Magistretti:** None.

Poster

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Increased depression-like behavior in response to stress in a mouse model with mitochondrial complex I dysfunction

Authors: *T. L. EMMERZAAL[1], M. ROELOFS[1], B. GEENEN[1], K. SCOTT[2], B. GRAHAM[3], W. CRAIGEN[3], G. MING[3], E. MORAVA[2], R. RODENBURG[4], T. KOZICZ[1,2];

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Abstract: Depression has long been thought to be caused by a decrease in monoamines, from which the serotonin hypothesis is the most prominent one. Recently the hypothesis that suboptimal mitochondrial function contributes to the pathobiology of depression has been put forward. To test this hypothesis, a new genetically engineered mouse model was generated with decreased mitochondrial function. These animals have a mutant Ndufs4 allele that consists of a gene trap insertion in an early intron of the locus. This results in a premature termination of the coding sequence and deficiency of the NDUFS4 protein. As a small amount of wild type protein is still produced, these animals are viable beyond 18 months of age, unlike constitutive Ndufs4 knockouts that die by 8 weeks of age. Ndufs4 encodes a structural subunit of complex I, an essential component of the electron transport chain and oxidative phosphorylation. This specific mutation leads to a 70% reduction of complex I activity. To test the hypothesis that suboptimal mitochondrial function is involved in the etiology of depression, Ndufs4 deficient and wild-type animals were either subjected to acute stress or chronic variable stress. We found that these transgenic animals show increased depression-like behavior as reflected by increased immobility in the Porsolt swim test. No differences were found in anxiety using the marble burying and novelty suppressed feeding tests. Also no differences were found in plasma corticosterone measurements between wild-type and deficient animals. On the other hand, preliminary data show a decreased neuronal activation in the central amygdala, investigated by cFos expression, an immediate early gene involved in neuronal activation. This decreased neuronal activation was however not found in the paraventricular nucleus of the hypothalamus. Overall, these results support the hypothesis that impaired mitochondrial function increases the risk to develop depression.

Disclosures: T.L. Emmerzaal: None. **M. Roelofs:** None. **B. Geenen:** None. **K. Scott:** None. **B. Graham:** None. **W. Craigen:** None. **G. Ming:** None. **E. Morava:** None. **R. Rodenburg:** None. **T. Kozicz:** None.

Poster

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: NIH Grant MH093362

Title: Role of the microglial T cell death associated gene-8 (TDAG8) receptor in depression-like behavior

Authors: *L. L. VOLLMER, R. AHLBRAND, S. N. SCHMELTZER, R. SAH;
Psychiatry and Behavioral Neurosci., Univ. Of Cincinnati, Cincinnati, OH

Abstract: Recent evidence suggests that immune dysfunction may play a role in the pathophysiology of depression. Pro-inflammatory cytokines, including TNF alpha (TNF-α), interleukin 6 (IL-6) and, interleukin IL-1β, are increased in plasma and cerebral spinal fluid (csf) of depressive subjects. These cytokines are mediators of sickness behavior, and have been found to influence the progression and severity of depression. Immune-modulatory targets are therefore important for understanding the pathophysiology of depression. The T cell death associated gene-8 (TDAG8) receptor is a proton-sensing G-protein-coupled receptor (GPCR) expressed on immune cells in both the CNS and periphery. Our previous work has shown modulation of inflammatory cytokine IL-1β by the TDAG8 receptor in the central nervous system (CNS). Given the link between depression and inflammation, the present study was undertaken to investigate the role of TDAG8 in depression relevant behaviors. TDAG8-deficient (TDAG8-/-) mice were screened in the forced swim test (FST) and sucrose preference paradigm. A significant reduction of immobility in the FST was observed in TDAG8-/- mice compared to wild type (TDAG8+/+) mice. These differences were not due to genotype induced alterations in motor activity as TDAG8+/+ and TDAG8-/- mice displayed similar activity in the home cage or novel context. TDAG8-/- mice showed significantly higher consumption of sucrose compared to TDAG8+/+ mice, although sucrose preference was not significantly different between genotypes. Ongoing studies are investigating the role of TDAG8 in behavioral outcomes following chronic mild stress, a rodent model of depression, complimented with neurochemical endpoints such as cfos and microglial activation. Although further validation is warranted, our preliminary results suggest an association of the TDAG8 receptor with depression-like behavior and its potential as an immune-modulatory target in depression. Support from R01 MH093362

Disclosures: **L.L. Vollmer:** None. **R. Ahlbrand:** None. **S.N. Schmeltzer:** None. **R. Sah:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Consultant for Ono Pharmaceuticals, Japan.

Poster

774. Mood Disorders: Antidepressants II

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: CIHR

CFI

Title: Impaired executive function and a depressive-like phenotype in gabra5-/- mice

Authors: ***S. W. KEMP**[1], N. K. CHAN[2], M. MILENKOVIC[2], A. J. RAMSEY[2], E. SIBILLE[2], B. ORSER[2];
[1]Dept. of Physiol., [2]Univ. of Toronto, Toronto, ON, Canada

Abstract: Background: Accumulating evidence suggests that reduced function of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) contributes to the pathogenesis of mood disorders. Patients with major depression have reduced GABA levels in the brain, and the expression levels of extrasynaptic GABAA receptors are reduced in suicide victims. In particular, the α5 subtype GABAA receptor is implicated in both depression and anxiety-related disorders. Here, we sought to determine whether reduced expression of α5GABAA is associated with depression and/or an anxiogenic behavioral phenotype in mice. Mice were also assessed on executive function memory tasks, which have been shown to be impaired in patients with mood disorders. We postulated that a decrease in α5 expression would lead to increases in depressive-like and anxiogenic behavior, and impaired executive function. Methods: Approval from the local animal care committee was obtained for all experiments. Males and females were evaluated. Mice were randomly assigned to one of two treatment groups (n=10 per group): α5 wildtype (Gabra5+/+), or α5 knockout (Gabra5-/-). Animals were serially assessed in a battery of behavioral tests which included: (1) open field test (OFT); (2) light-dark maze; (3) puzzle box; (4) elevated plus maze (EPM); (5) forced swim test (FST), and; (6) tail suspension test (TST). The same cohort of animals was tested on each behavioral paradigm. Results: Gabra5-/- mice display a depressive-like phenotype when compared to Gabra5+/+ animals as evidenced by tests of behavioral despair such as the TST [$t(17)=2.98$, $p<0.01$]. In addition, results from the puzzle box task indicate that Gabra5-/- animals are cognitively impaired compared to Gabra5+/+ animals in measures of executive functioning [$t(17)=2.83$, $p<0.01$]. Interestingly, sexual dimorphism was displayed in this assessment, with female animals displaying increased memory and executive function irrespective of genetic condition [$t(17)=2.7$, $p<0.05$]. Conclusion: A genetic knockdown of α5GABAA receptors leads to a depressive-like and cognitively impaired phenotype in mice. These results suggest that pharmacological manipulation that selectively upregulates extrasynaptic α5GABAA receptors may provide a novel treatment strategy for patients with depression.

Disclosures: **S.W. Kemp:** None. **N.K. Chan:** None. **M. Milenkovic:** None. **A.J. Ramsey:** None. **E. Sibille:** None. **B. Orser:** None.

Poster

774. Mood Disorders: Antidepressants II

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: KAKENHI 26860943

Title: Evaluation of home cage social behaviors in mutant mitochondrial DNA polymerase transgenic mice

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Dokkyo Med. Univ. Sch. of Med., Tochigi, Japan

Abstract: Mutant mitochondrial DNA polymerase (POLG) transgenic (Tg) mice that express mutant POLG with defective 3'-5' exonuclease activity under the promoter of calcium/calmodulin dependent protein kinase II α were reported to demonstrate forebrain specific accumulation of multiple deleted mitochondrial DNA, mood disorder-like phenotypes, and periodic wheel-running activity pattern associated with estrous cycle. In this study, we evaluate the long-term home cage social behaviors and anhedonic-like behavior of Tg mice. For behavioral observation, six pairs of 20-week old female Tg mice and control C57BL/6J (B6) mice were housed on a 12 h light/dark cycle (lights on between 6:00 and 18:00) and used for experiments. A heterozygous Tg mouse was paired with a female wild-type sibling, which had been cagemates since weaning, and bred in a polycarbonate cage (22 × 32 × 13.5 cm) with a transparent lid for 24 days. Home cages were consecutively recorded using digital video cameras which were placed above the cage and eligible for recording at night. The video files of the first hour of dark phase were analyzed every other day. The total duration and frequency of behaviors in Tg pairs were blind scored to rate aggressive behaviors (chase, food competition, boxing posture), non-aggressive behaviors (huddle, allogrooming, body contact), non-social behaviors (feeding, self-grooming) using Solomon Coder beta 15.03.15 and were compared with those in B6 control pairs. Social interaction test with unfamiliar female mouse was conducted the day after the end of the 24-day observation (day 25). Sucrose preference was tested using two-bottle choice procedure between bottle containing a 1% sucrose solution and water-containing bottle for 2 days (day 27, 28) after 2-day habituation. The whole study was formally approved by the animal care and use committee of Dokkyo Medical University School of Medicine. The

behavioral observation of matched pairs of Tg and B6 mice in home cage revealed that Tg mice showed significantly longer duration of food competition ($p = 0.012$) and nose to body contact for their cagemates ($p = 0.049$) as compared in B6. Tg mice also significantly chased their cagemates more frequently than B6 did ($p = 0.022$). In contrast, Tg mice spent significantly less time in self-grooming compared with B6 ($p = 0.019$). There were no significant differences between Tg and B6 in the time spent in the interaction zone in social interaction test. In sucrose preference test, sucrose consumption also showed no significant difference between Tg and B6. These results indicate mutant POLG Tg mice show manifestation of high levels of aggressive social interactions in the home cage environment.

Disclosures: G. Kuratomi: None. **Y. Arime:** None. **S. Suzuki:** None. **K. Akiyama:** None.

Poster

774. Mood Disorders: Antidepressants II

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 774.20/G24

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: KAKENHI 24650223

Takeda Pharmaceutical Company Limited

Title: Impaired hippocampal reward-related activity in the DISC1 mutant mice

Authors: *Y. HAYASHI[1], A. SAWA[3], T. HIKIDA[2];
[2]Med. Innovation Ctr., [1]Kyoto Univ. Grad. Sch. of Med., Kyoto, Japan; [3]Dept. of Psychiatry and Behavioral Sci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Cognitive deficit is one of the symptoms of mental disorders, and the deficit seem to result from an inability to integrate information in the neural systems. We showed that a transgenic mouse expressing a dominant-negative form of DISC1, a risk gene for neuropsychiatric disorders, exhibited impaired performance in reward-place association task only when combined with a mild isolation stress. Previous studies show that hippocampal CA1 cells exhibit an elevated activity at reward zone as well as their place field activity during the task, suggesting that the hippocampus is one of the integration site for multiple information. CA1 cells in the mutant mice showed normal place cell property, but their activity at reward zone was diminished. This abnormality in hippocampal activity may underlie the learning deficit of the mutant mice.

Disclosures: **Y. Hayashi:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Takeda Pharmaceutical Company Limited. **A. Sawa:** None. **T. Hikida:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution; Takeda Pharmaceutical Company Limited.

Poster

774. Mood Disorders: Antidepressants II

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 774.21/G25

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: MIUR Prin 2008, 200894SYW2

Toscana Life Sciences Foundation Orphan_0108 program

Title: Serotonin depletion affects serotonergic neuronal circuits in adult mice

Authors: ***M. PRATELLI**[1], B. PELOSI[1,2], S. MIGLIARINI[1], M. PASQUALETTI[1,3]; [1]Univ. of Pisa, Pisa, Italy; [2]Lab. of Neural Differentiation, Inst. of Neuroscience, UCL, Brussels, Belgium; [3]Cnt. for Neurosci. and Cognitive Systems, Inst. Italiano di Tecnologia, Rovereto, Italy

Abstract: Serotonin is a neurotransmitter synthesized in two steps with tryptophan hydroxylase 2 (Tph2) as the rate-limiting enzyme and it is implicated in the modulation of numerous physiological processes including mood, sleep, aggressivity and sexual behavior. Serotonergic neurons provide a profuse innervation to the whole CNS. The synthesis of serotonin and the expression of its receptors early in embryonic development, as well as its maternal and placental sources to the foetus, have led to the hypothesis that serotonin could act as a growth regulator in specific developmental events such as neurogenesis, neuronal migration and circuitry formation. However, the precise role of serotonin in specific morphogenetic activities during CNS development remains poorly understood. To address the consequences of time-controlled serotonin depletion on CNS development, we have generated a Tph2 conditional (floxed) allele and used it in combination with a Tph2-GFP knockin mouse line allowing the visualization of serotonergic neurons and fibers (Migliarini et al., 2013). Besides the severe abnormalities in the serotonergic circuitry formation observed in Tph2 knockout mice, serotonin depletion in adult animals induces an increase of the density of serotonergic fibers projecting to the hippocampus.

These results show that the mature serotonergic system exhibits a previously unexpected plasticity and that appropriate serotonin homeostasis is crucial not only for proper development of the serotonergic neuronal circuit but also for its maintenance during adulthood. Migliarini et al. Mol Psychiatry 2013 18: 1106-18.

Disclosures: **M. Pratelli:** None. **B. Pelosi:** None. **S. Migliarini:** None. **M. Pasqualetti:** None.

Poster

774. Mood Disorders: Antidepressants II

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 774.22/G26

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: R01DA035371

Title: Decreased somatostatin expression and behavioral abnormalities in a somatostatin-IRES-CRE mouse line

Authors: ***S. MOLAS**, P. GARDNER, A. TAPPER;
Brudnick Neuropsychiatric Res. Institute, Dept. of Psychiatry, Univ. of Massachusetts Med. Sch., Worcester, MA

Abstract: Somatostatin (Sst) is a modulatory neuropeptide frequently expressed by GABAergic neurons. The role of Sst-positive inhibitory neurons has recently been studied using the knock-in transgenic mouse line Sst-IRES-Cre (Jackson labs stock number: 13044), which harbors an internal ribosome entry site and the Cre recombinase gene within the Sst locus. Therefore, this line is expected to drive Cre expression under the Sst promoter without altering the endogenous levels of Sst. However, few investigations have addressed the validity and reliability of this Cre-driven model. The present study demonstrates that mice homozygous for the Cre allele ($Sst^{Cre+/+}$) exhibited significantly reduced levels of endogenous Sst as compared to their wild type (WT) littermates ($SSt^{Cre-/-}$). The loss of Sst expression could be observed in the hippocampus and cortex, from P0 to P60, and appears to be compensated by an upregulation of the Sst receptors. Behaviorally, adult $Sst^{Cre+/+}$ male mice exhibited reduced locomotor activity during the active phase of the circadian cycle, similar to Sst knockout mice. Moreover, in the elevated plus maze $Sst^{Cre+/+}$ mice spent less time in the open arms compared to WT mice indicating increased baseline anxiety levels. By contrast, female $Sst^{Cre+/+}$ mice were hyperactive towards the end of the active phase of the circadian cycle. In addition, they spent similar time in the open arms of the elevated plus maze indicating normal anxiety-like response. Importantly, in both male and

female mice, the expression of Sst and behavioral abnormalities were partially rescued in the heterozygous $SSt^{Cre+/-}$ littermates. To determine if Cre expression in the Sst-IRES-Cre line was appropriately restricted to neurons expressing Sst, we crossed $Sst^{Cre+/+}$ mice with an Ai9 td-Tomato reporter strain. The double transgenic offspring expressed the red fluorescent protein in the majority of Sst immunopositive neurons. However, tomato red was detected in Sst immunonegative neurons within several brain areas including those not reported to express Sst. In summary, our study reveals important alterations in the Sst-IRES-Cre mouse line including behavioral abnormalities and Cre driving expression in non-Sstergic neurons that could lead to experimental misinterpretations, especially when working with homozygous animals.

Disclosures: S. Molas: None. **P. Gardner:** None. **A. Tapper:** None.

Poster

774. Mood Disorders: Antidepressants II

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

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Independent Investigator Award from the National Alliance for Research on Schizophrenia and Depression

Title: Enhanced adult hippocampal neurogenesis via regulation of perforant path activity: a novel treatment for stress- induced depression?

Authors: *S. YUN[1], P. D. RIVERA[1], R. REYNOLDS[1], N. ITO[1], B. L. ROTH[2], D. M. CHETKOVICH[3], A. J. EISCH[1];
[1]UT Southwestern Med. Ctr., Dallas, TX; [2]Northwestern Univ., Chicago, IL; [3]Univ. of North Carolina, Chapel Hilll, NC

Abstract: A major problem with current antidepressants is that ~50% of patients will relapse. A better understand of the neural circuitry underlying depressive behaviors and antidepressive treatments will help us develop more effective treatments for Major Depressive Disorder (MDD). Recent studies – including those showing decreased hippocampal dentate gyrus (DG) progenitors and neuron number in unmedicated humans with MDD, and the requirement of adult DG neurogenesis for certain effects of antidepressants in some strains of rodents – suggest that enhancement of hippocampal neurogenesis may be a useful treatment for depression. Our hypothesis is that controlled enhancement of DG input via the glutamatergic perforant path (PP) is antidepressive via increased DG neurogenesis. While entorhinal cortex (Ent) deep brain stimulation and thus PP activation improves spatial memory and enhances DG neurogenesis (Stone et al., 2011), it is unknown whether Ent stimulation can also be antidepressive. We used two independent methods to stimulate PP activity and/or increase excitability of Ent Layer II stellate neurons in rodents: Ent knockdown of the brain-specific hyperpolarization-activated cyclic nucleotide-gated (HCN) channel auxiliary subunit TRIP8b, and PP stimulation via the chemogenetic Designer Receptors Exclusively Activated by Designer Drugs (DREADD) technology. Thus far, the results support our hypothesis. For example, knockdown (KD) of Ent TRIP8b increases hippocampal neurogenesis and promotes neuronal maturation, and also improves performance in behavioral measures of hippocampal dependent memory (e.g. CFC) and antidepressant efficacy (e.g. FST). Moreover, enhanced neurogenesis induced by Ent TRIP8b KD is required for antidepressant efficacy. As a cell type specific approach, enhanced excitability of glutamatergic neurons – via stereotaxic infusion of AAV-hM3Dq-mcherry into medical and lateral Ent Layer II - enhances hippocampal neuroplasticity. We are currently examining whether enhanced stellate cell excitability is antidepressant. Also, we are screening what molecular pathway in the DG plays role in antidepressant via enhanced DG activity using unbiased approach. These results will reveal whether highly promising targets for the treatment of depression – DG neurogenesis and PP activity – work together to regulate affective behaviors. In addition to exploring this novel connection and suggesting better paths for treatment, these aims will notably advance our understanding of the molecular, cellular, and neuro-circuit level regulation of depression-related behaviors.

Disclosures: S. Yun: None. **P.D. Rivera:** None. **R. Reynolds:** None. **N. Ito:** None. **B.L. Roth:** None. **D.M. Chetkovich:** None. **A.J. Eisch:** None.

Poster

774. Mood Disorders: Antidepressants II

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: DFG grant BA 1582/2-1

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Lichtenberg Professorship Award of the Volkswagen Foundation

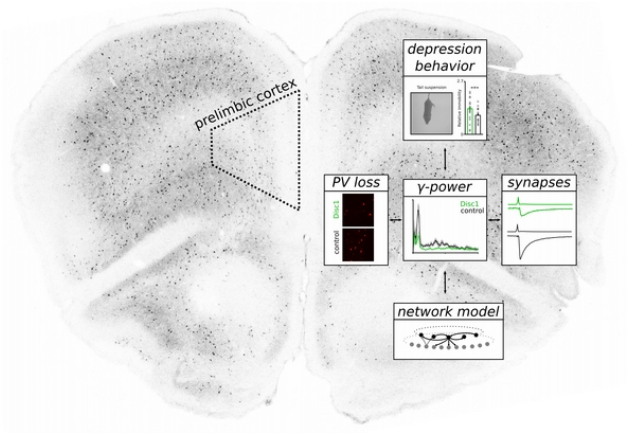
Scottish Northern Research Partnership

Spemann Graduate School for Biology and Medicine, Freiburg

Title: Impaired fast-spiking interneuron function in a genetic mouse model of depression

Authors: *J.-F. SAUER, M. STRUEBER, M. BARTOS;
Albert-Ludwigs Univ. Freiburg, Freiburg, Germany

Abstract: Rhythmic neuronal activity provides a frame for information coding by co-active cell assemblies. Abnormal brain rhythms are considered as potential pathophysiological mechanisms causing mental disease, but the underlying network defects are largely unknown. Here we show that mice expressing truncated Disrupted-in-Schizophrenia 1 (Disc1), which mirror a high-prevalence genotype for human psychiatric illness, show behavioral despair in broadly accepted assays of depression-related behavior in rodents. Theta and low-gamma synchrony in the prelimbic cortex (PrlC) are impaired in Disc1 mice and inversely correlated with the extent of behavioral despair. While weak theta activity is driven by the hippocampus, disturbance of low-gamma oscillations is caused by local defects of parvalbumin-expressing fast-spiking interneurons: First, the number of fast-spiking interneurons is reduced in the prelimbic cortex of Disc1 mice. Second, these neurons receive fewer excitatory inputs. Finally, Disc1 fast-spiking interneurons form fewer release sites on their target principal cells. Computational analysis indicates that weak excitatory input and inhibitory output of fast-spiking cells may lead to impaired gamma oscillations. Our data therefore link network defects with a risk gene mutation underlying depression in humans.



Disclosures: **J. Sauer:** None. **M. Strueber:** None. **M. Bartos:** None.

Poster

774. Mood Disorders: Antidepressants II

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 774.25/G29

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: NSERC Grant 311763-07

Title: Chronic lithium treatment rescued Akt3 KO mice depressive and anxiety-like behaviors

Authors: ***Y. BERGERON**, G. BUREAU, M.-É. LAURIER-LAURIN, E. ASSELIN, G. MASSICOTTE, M. CYR;
Med. biology, Univ. du Quebec a Trois-Rivieres, Trois-Rivieres, QC, Canada

Abstract: The protein kinase B (PKB/Akt) is found in three distinctive isoforms: PKBα/Akt1, PKBβ/Akt2, and PKBγ/Akt3. Although they display high homology and similar structural organization, recent findings illustrate that each of these isoforms play distinctive physiological role. Akt3 is well expressed in the brain and is critical for postnatal brain development, suggesting this isoform could play a role in cerebral functions. In this study, we have investigated the impact of Akt3 deletion on behaviors, synaptic plasticity and biochemical signaling. First, our results show that cognitive functions remained intact in the Akt3 KO mice, since no difference is observed in two different cognitive tests related to the hippocampus, the Morris water maze and the novel object recognition test. In addition, electrophysiology on Akt3 KO hippocampal slices shows that neither STP nor LTP levels is modified compared to WT hippocampal slices. However, Akt3 deletion induces several behavioral anomalies: reduced

prepulse inhibition, social behavior deficits as well as high level of depressive and anxiety-like behaviors. Biochemical investigations reveal that Ak3 deletion does not modulate levels of total Akt1 and Akt2 in the anterior cortex, striatum, hippocampus and cerebellum. However, levels of GSK3α/β phosphorylated at serine 21/9 are decreased in the anterior cortex, hippocampus, striatum and cerebellum of Akt3 KO mice; no change in levels of total GSK3α/β is observed. In order to verify whether the decreased phosphorylated GSK3α/β levels could be related to the observed depressive and anxiety-like behaviors, a lithium diet was chronically administrated to Akt3 KO and WT mice. Lithium is a mood modulator known to modulate GSK3α/β phosphorylation. This treatment increases levels of phosphorylated GSK3α/β and rescues the depressive and anxiety-like behaviors observed in Akt3 KO mice. These results suggest that GSK3α/β may contribute to the depressive and anxiety-like behaviors found in the Akt3 KO mice and support that an isoform-specific mechanism may define the neuronal signaling of Akt in psychiatric illnesses-related behaviors.

Disclosures: **Y. Bergeron:** None. **G. Bureau:** None. **M. Laurier-Laurin:** None. **E. Asselin:** None. **G. Massicotte:** None. **M. Cyr:** None.

Poster

775. Antidepressants: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 775.01/G30

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: ERC advanced grant

Sigrid Juselius Foundation

Orion-Farmos Reseach Foundation

Academy of Finland

Doctoral Programme Brain & Mind

Title: Isoflurane anesthesia activates TrkB neurotrophin receptor signaling and produces rapid antidepressant-like effects

Authors: ***H. ANTILA**[1], D. POPOVA[1], J. LINDHOLM[1], I. YALCIN[2], T. RANTAMÄKI[1], E. CASTRÉN[1];

[1]Neurosci. Ctr., Univ. of Helsinki, Helsinki, Finland; [2]Inst. of Cell. and Integrative Neurosciences, Strasbourg, France

Abstract: Brain-derived neurotrophic factor BDNF and its receptor TrkB are involved in the mechanism of action of conventional antidepressant drugs and rapid-acting antidepressant ketamine. Enhanced BDNF-dependent neuronal plasticity has been suggested to mediate the therapeutic effects of antidepressant drugs. Isoflurane, a commonly used volatile anesthetic, has been shown to produce rapid antidepressant effects in patients with treatment resistant depression. We have here investigated whether isoflurane activates signaling pathways known to be involved in the antidepressive effects in rodents. We have also studied the effects of isoflurane on neuronal plasticity and mouse behavior. Anesthetic dose of isoflurane rapidly activated TrkB receptor and increased signaling via mTOR pathway in the mouse prefrontal cortex and hippocampus. The phosphorylations of CREB, Akt, P70S6kinase, 4E-BP1 and GSK3beta were significantly increased after 30 minutes of isoflurane treatment. Isoflurane facilitated long-term potentiation in the hippocampus when measured 24 hours after the treatment. A single isoflurane treatment led to a rapid antidepressant-like behavioral effect in the forced swim test in wild-type mice but not in mice overexpressing the dominant-negative TrkB receptors, suggesting that the behavioral effects of isoflurane in the forced swim test are mediated via TrkB receptor. Furthermore, in the neuropathic pain model of depression a single isoflurane anesthesia rapidly normalized the anxiogenic phenotype in the novelty suppressed feeding test. In conclusion, single and brief treatment with commonly used anesthetic isoflurane produces molecular, functional and behavioral effects that resemble those produced by conventional antidepressant drugs and ketamine. These findings encourage studying further the potential of isoflurane anesthesia as a treatment option for major depressive disorder both in experimental models and human patients.

Disclosures: H. Antila: None. **D. Popova:** None. **J. Lindholm:** None. **I. Yalcin:** None. **T. Rantamäki:** None. **E. Castrén:** None.

Poster

775. Antidepressants: Animal Models

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: R01 MH086828

T31 GM008181

Title: Co-activation of multiple serotonin receptors underlies sustained potentiation of synaptic transmission by fluoxetine in the hippocampus

Authors: *A. M. VAN DYKE, A. J. KALLARACKAL, X. CAI, S. M. THOMPSON; Physiol., Univ. of Maryland, Baltimore, Baltimore, MD

Abstract: Serotonin (5-HT) and its receptors have long been major targets in the pharmacological treatment of depression. Despite their widespread use, the mechanism of action underlying the therapeutic efficacy of SSRIs like fluoxetine remains poorly understood. Our laboratory has shown that raising endogenous 5-HT can potentiate certain excitatory synapses, including those that are weakened in depression models, and that this potentiation is necessary for the therapeutic behavioral action of antidepressants. In the hippocampus, activation of G_i/G_o-coupled 5-HT_{1B} receptors potentiates glutamatergic signaling in temporoammonic (TA) to CA1 pyramidal cell synapses in the stratum lacunosum-moleculare (SLM). This occurs due to the phosphorylation of the AMPA receptor subunit GluA1 at serine 831 via recruitment of the Phospholipase C/Ca2+/Calmodulin-dependent Protein Kinase II (PLC/Ca2+/CaMKII) signaling cascade. Selective activation of 5HT1BRs produces a *transient* potentiation, whereas elevation of endogenous 5-HT with the SSRI fluoxetine *persistent* potentiates TA-CA1 synapses in a 5HT1BR-dependent manner. We hypothesized that fluoxetine's sustained potentiation of hippocampal TA-CA1 synapses is due to the co-activation of 5-HT_{1B}R and a G_S-coupled serotonin receptor causing activation of PKA signaling. We have addressed this hypothesis by using various pharmacological tools to disrupt/activate specific receptors and their respective signaling pathways. We have observed that antagonists of 5-HT_{1B}Rs prevents the potentiation of TA-CA1 field potentials by both fluoxetine and anpirtoline. Disruption of PKA signaling had no effect on 1B-mediated potentiation but inhibition of PKA did prevent the sustained potentiation by fluoxetine. Antagonists of the various G_s-coupled 5-HTRs revealed that 5-HT_6R was underlying this activation of PKA by fluoxetine, whereas 5-HT_4R or 5-HT_7R antagonists had no effect. Conversely, co-activation of 5-HT_{1B}Rs and 5-HT_6Rs, with their respective agonists, produced a sustained increase in synaptic transmission. Western blotting is in progress to determine the time course of kinase activation and AMPA receptor phosphorylation under different conditions. Taken together these data suggests that the SSRI fluoxetine raises endogenous 5-HT resulting in the co-activation of multiple 5-HTRs to produce an increase in glutamatergic transmission. 5-HT_{1B}R activation initially induces the increase in synaptic strength through PLC/Ca2+/CaMKII dependent phosphorylation of AMPA receptors and 5-HT_6R activation maintains this increase through the recruitment of PKA signaling.

Disclosures: **A.M. Van Dyke:** None. **A.J. Kallarackal:** None. **X. Cai:** None. **S.M. Thompson:** None.

Poster

775. Antidepressants: Animal Models

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Program#/Poster#: 775.03/G32

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: CNPq Grant 308723/2013-9

CAPES

Title: Ursolic acid protects against depressive-like behavior induced by chronic unpredictable stress and *in vitro* corticosterone-induced reduction on cell viability

Authors: *A. S. RODRIGUES, A. B. R. HRYB, A. R. S. COLLA, N. PLATT, V. LIEBERKNECT, F. L. PAZINI, M. P. CUNHA, M. P. KASTER;
Univ. Federal de Santa Catarina, Florianopolis, Brazil

Abstract: Ursolic acid (UA), a pentacyclic triterpenoid, exhibits antidepressant-like effects in behavioral tests predictive of antidepressant activity. This study investigated its ability to prevent the depressive-like behavior induced by chronic unpredictable stress (CUS), an animal model that mimics human depression. Additionally, its ability to counteract the corticosterone-induced reduction on cell viability in mouse hippocampal neuronal cell line was also evaluated. All experiments were approved by the Ethics Committee of the Institution. Male Swiss mice (60 day-old, 40-45 g) were submitted to CUS procedure during 14 days. In the last 7 days, mice received UA (0.1 mg/kg, p.o.) or fluoxetine (10 mg/kg, p.o., positive control). On 15th day, immobility time, anhedonic behavior and locomotor activity were evaluated in the tail suspension test (TST, 6-min session), splash test (5-min session) and open-field test (6-min session), respectively. The mRNA expression of anti-apoptotic (Bcl-2) and pro-apoptotic (Bax) proteins in hippocampal tissue was evaluated using qRT-PCR. For *in vitro* experiments, HT22 cells were subcultured in 96-well plates at a seeding density of 6 × 103 cells per well. Cells were pretreated during 48 h with UA (5, 15 μM) or vehicle (DMSO 0.1%) in DMEM with 10% FBS and 24 h after with corticosterone (50 μM) or vehicle. Cell viability was measured by a colorimetric assay with MTT. Results were analyzed by two-way ANOVA followed by Newman-Keuls test, when appropriate (significant when $p<0.05$). Repeated treatment with UA prevented the depressive-like behavior (increased immobility time in the TST and latency to grooming in the Splash Test) without altering locomotor activity of mice. UA also prevented the increased hippocampal Bax mRNA expression and the decreased Bcl-2/Bax mRNA ratio caused by CUS. The *in vitro* assays showed that incubation with UA (5, 15 μM) alone during 48 h did not alter hippocampal neuronal viability, but was able to prevent the reduction in cell viability induced by corticosterone (50 μM). The results indicate a robust effect of UA in reversing

behavioral and biochemical alterations induced by CUS in mice and to protect against corticosterone-induced cell viability in mouse hippocampal neuronal cell line.

Disclosures: **A.S. Rodrigues:** None. **A.B.R. Hryb:** None. **A.R.S. Colla:** None. **N. Platt:** None. **V. Lieberknect:** None. **F.L. Pazini:** None. **M.P. Cunha:** None. **M.P. Kaster:** None.

Poster

775. Antidepressants: Animal Models

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Program#/Poster#: 775.04/G33

Topic: C.19. Drug Discovery and Development

Title: Amantadine reduces depressive behavior in rodent models of depression

Authors: *J. NGUYEN, B. BRIGHAM;
Adamas Pharmaceuticals, Inc., Emeryville, CA

Abstract: Amantadine HCl is an NMDA receptor (NMDAr) antagonist approved for the treatment of influenza and Parkinson's disease. In addition to its glutaminergic activity, amantadine has also been shown to modulate other neurotransmitter systems, inhibit microglial activation, and elevate levels of brain-derived neurotrophic factor (BDNF). Amantadine has also been shown to have antidepressant properties in animal models of depression and in small clinical trials. Recently, ketamine, another NMDAr antagonist, has been shown to produce a rapid antidepressant response in patients with treatment-resistant depression. In clinical trials, the antidepressant effect of a single dose of ketamine was significant within an hour of administration and can last up to 7 days. In several models of depression in rodents, a single dose of ketamine alleviates depressive behavior whereas a single dose of standard antidepressants (ie, a selective serotonin uptake inhibitor, SSRI, or a tricyclic antidepressant, TCA) has no effect. However, ketamine also has dissociative properties and abuse liabilities, limiting its overall use as an antidepressant. Here, we characterized the antidepressant properties of amantadine using multiple models of depression and determined the time of onset of antidepressant activity. First, in the chronic social defeat model, male C57BL/6J mice were subjected to daily aggression by CD-1 mice over a period of 10 days, which produced enduring and clinically relevant depressive phenotypes such as social avoidance, reduced locomotion, and anhedonia. Second, in the forced swim test, male Sprague-Dawley rats were placed in a container of water and the immobility time, a measure of despair, was recorded over a 5 minute interval. We demonstrate that amantadine when administered in repeated doses produced a statistically significant antidepressant effect. More importantly, when administered in a single acute dose, amantadine

reduced depressive symptoms in a dose-dependent fashion whereas fluoxetine (an SSRI) had no effect. Together, the data suggest that amantadine may have clinical utility as an antidepressant with a rapid onset of activity, and provide a framework for further clinical evaluation.

Disclosures: J. Nguyen: A. Employment/Salary (full or part-time):; Adamas Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Adamas Pharmaceuticals. **B. Brigham:** A. Employment/Salary (full or part-time):; Adamas Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Adamas Pharmaceuticals.

Poster

775. Antidepressants: Animal Models

Location: Hall A

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Program#/Poster#: 775.05/G34

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: NLRP3 inflammasome is activated by psychological stress: a potential role of NLRP3 inhibitor beta-hydroxybutyrate's antidepressant effect

Authors: *T. YAMANASHI[1], M. IWATA[1], N. KAMIYA[1], T. YAMAUCHI[1], R. S. DUMAN[2], K. KANEKO[1];
[1]Tottori Univ., Tottori, Japan; [2]Yale Univ. Sch. of Med., New Haven, CT

Abstract: Stress decreases neurogenesis and synaptogenesis in the adult hippocampus, contributing to depressive-like behaviors in rodent models, but the mechanisms by which stress causes neuronal damage remain unknown. We have previously reported that interleukin-1beta (IL-1beta) decreases neurogenesis and causes depressive behavior. We have also demonstrated that stress increases ATP and IL-1beta in the hippocampus, and that administration of the purinergic P2X7 receptor (P2X7R) antagonist (A-804598) ameliorates both of these effects of IL-1beta in the hippocampus, as well as decreased neurogenesis and depressive behavior caused by stress. Activation of microglia and inflammatory responses also occurs via pathogen and damage associated molecular patterns (PAMPs and DAMPs) that bind to toll like receptors; when combined with ATP-P2X7R triggered K+ efflux, this leads to the induction of large multi-protein complex termed the NLRP3 inflammasome, and mature IL-1beta is released. These findings indicate that ATP release plays a critical role in stress-induced inflammatory responses and depressive behavior, but direct evidence for ATP and NLRP3 in the effects has not been demonstrated. Here, we investigated how ATP stimulates IL-1beta release, and developed a new

strategy for the treatment of depression. We hypothesized that psychological stress activates NLRP3 inflammasome via ATP elevation. We confirmed that immobilization stress activates NLRP3 inflammasome in the adult rat hippocampus, as measured by a co-immunoprecipitation-western blotting method. We also confirmed that A-804598 ameliorates NLRP3 inflammasome activation induced by immobilization stress. We are currently investigating whether inhibitors of NLRP3, notably beta-hydroxybutyrate (BHB), have antidepressant and anxiolytic actions. BHB is a ketone body that supports mammalian survival during states of energy deficit. Recently it has been reported that BHB suppresses activation of the NLRP3 inflammasome in response to ATP by preventing K+ efflux and reducing NLRP3 oligomerization. Preliminary studies indicate that BHB administration prevents anxiolytic behaviors induced by chronic unpredictable stress in rodents. These studies are consistent with the hypothesis that NLRP3 inhibitors are novel targets for antidepressant drug development.

Disclosures: **T. Yamanashi:** None. **M. Iwata:** None. **N. Kamiya:** None. **T. Yamauchi:** None. **R.S. Duman:** None. **K. Kaneko:** None.

Poster

775. Antidepressants: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 775.06/G35

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: Academy of Finland

Title: Validation of a rat model of therapy resistant major depressive disorder and investigation of resistance-associated changes of the brain-derived neurotrophic factor BDNF

Authors: W. THEILMANN[1,2], W. LÖSCHER[1,3], H. FRIELING[4,3], S. BLEICH[4,3], M. RHEIN[4,3], N. MATSUI[5,6], S. KOHTALA[5], C. BRANDT[1,3], *T. P. RANTAMAKI[5];
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Abstract: About 30% of people suffering from major depressive disorder (MDD) do not achieve remission with antidepressant drugs (AD). For the development of novel antidepressant treatments and the understanding of pathophysiological mechanisms underlying therapy

resistance, valid animal models of therapy-resistant MDD are of special interest. Christensen et al. (2011, Neuroscience,196:66-79) exposed rats to chronic mild stress (CMS) and selected rats which responded or did not respond to the AD citalopram, thereby proposing an animal model for pharmacoresistant MDD. In the present study we pursued two aims: 1) To further determine the predictive validity of the model, 2) to correlate therapy efficacy with changes of the brain-derived neurotrophic factor (BDNF). Pharmacoresistant MDD patients often respond to electroconvulsive therapy. Therefore we compared chronic citalopram treatment and electroconvulsive stimulations (ECS) in rats, to test whether clinical response patterns can also be found in the experimental setting. Male Wistar rats were exposed to CMS for 21 days before the onset of treatment. CMS was continued during treatment period. The selection of responders and nonresponders was based on anhedonic-like behavior measured by the sucrose consumption test (SCT). Moreover, we established an evaluation tool according to the Hamilton Rating Scale for Depression (HAM-D), which measures the severity of a set of symptoms such as motivation and anxiety. Therefore, we performed the open field test, the novelty induced hypophagia test, the forced swim test (FST), and the social interaction test. Finally, we compared the Bdnf-DNA methylation and BDNF protein expression levels in blood, prefrontal cortex and hippocampus of treatment responders and nonresponders. Based on the SCT, we observed resistance to citalopram, but a high response rate to bifrontal ECS applied via cortical screw electrodes. The response rate was much lower when all tests were taken into account. Further, there was a high variation in the response rate depending on the test performed. The tests with the most homogeneous outcome were the SCT and FST. No correlation between treatment response and BDNF changes could be detected. The CMS model seems to have a high predictive value for therapy-resistant MDD. The classification of resistant and responsive rats depends on the underlying test to determine depressive-like behavior. This could bias subsequent investigations such as molecular or biochemical changes. Further, selection of responders and nonresponders minimizes group size and could be an explanation why we did not find a correlation between BDNF changes and therapy response.

Disclosures: **W. Theilmann:** None. **W. Löscher:** None. **H. Frieling:** None. **S. Bleich:** None. **M. Rhein:** None. **N. Matsui:** None. **S. Kohtala:** None. **C. Brandt:** None. **T.P. Rantamaki:** None.

Poster

775. Antidepressants: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 775.07/G36

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Chronic social defeat mouse assay for assessing anti-depression therapies

Authors: *J. T. PUOLIVALI[1], S. ALASTALO[1], A. NURMI[1], O. KONTKANEN[1], B. HENGERER[2], K. A. ALLERS[2];
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Abstract: The current paradigms for testing anti-depression therapies have little face validity and predictive validity within only a very narrow range of mechanisms of action and a narrow therapeutic window. The chronic social defeat (CSD) model is ethologically relevant and has robust depressive-like endpoints. Moreover, the paradigm allows for either chronic or acute anti-depressant treatments with any specified dosing paradigm. Depressed patients have elevated levels of blood-brain-barrier penetrant cytokines in brain. In addition, depressed patients have elevated microglia, and elevated levels of quinolinic acid suggesting the induction of microglial indoleamine 2,3-dioxygenase 1 (IDO1). It has been shown that depending on concentration, quinolinic acid can either be helpful or harmful to neurons, and that excess quinolinic acid can interfere with neural transmission in circuits known to be involved in depressive symptoms. The purpose of this study was to test the efficacy of IDO1 inhibitors, IDO1A and IDO1B in the CSD model paradigm in C57Bl/6J male mice. The mice were exposed to chronic stress by aggressor mice (CD-1 retired breeders) for period of 15 days. Starting from day 14, mice were subjected open field (OF), contextual fear conditioning (CFC), and the active avoidance (AA) tests to monitor stress related changes in behavior compared to the control mice. The compounds were administered once-a-day starting from CSD day 13. In a separate experiment, the control and defeated mice were tested in the sucrose preference test (SPT). Following 15 days of CSD, the mice displayed clear and robust depressive-like phenotypes. These included: decreased sucrose preference, reduced activity and increased immobility in OF, increased freezing behavior in the CFC test, and impaired avoidance behavior in the AA assay. Moreover, treatment with IDO1B significantly decreased freezing in CFC test compared to vehicle treated CSD mice. Finally, post-mortem samples can be used to validate the target of interest, for example induction of IDO1, microglia activation, and tryptophan catabolite presence following IDO1 inhibition. In conclusion, the multiple endpoints of the CSD model provide a comprehensive model of depression in which the next generation anti-depressant can be assessed.

Disclosures: J.T. Puolivali: None. **S. Alastalo:** None. **A. Nurmi:** None. **O. Kontkanen:** None. **B. Hengerer:** None. **K.A. Allers:** None.

Poster

775. Antidepressants: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 775.08/G37

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: Antidepressant actions of deep brain stimulation are augmented by dopamine reuptake inhibition

Authors: *R. P. KALE[1], A. Z. KOUZANI[2], K. WALDER[3], M. BERK[3], S. J. TYE[1];
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Abstract: The mechanisms underlying treatment resistant depression (TRD) and manic switch are yet to be fully understood. A diminished plasticity response is suggested to be a neuroprogressive adaptation to treatment resistance in TRD, and may be alleviated by DBS. TRD can be induced in rodents through a stress-hormone challenge using adrenocorticotropic hormone (ACTH). TRD is often characterized by lower psychomotor activity, alterations in metabolism, reduced motivation, anhedonia, passivity and decreased positive affect. Modulation of dopamine sensitivity within the cortico-mesolimbic system, particularly the nucleus accumbens (NAc) and medial forebrain bundle (mfb), mediate coping behaviors in response to stress. This study aims to quantify antidepressant actions of NAc and mfb DBS in ACTH-pretreated animals, alone and in interaction with dopamine reuptake inhibition. TRD was induced in male Wistar rats via ACTH treatment (ACTH-(1-24); i.p. 100µg/day) in combination with social isolation (2 weeks). A control group was similarly isolated and treated with saline (i.p. 0.9%/day). ACTH and saline treated rats were further divided into 2 main groups: 1) receiving the dopamine reuptake inhibitor GBR12909 (GBR) daily during the second treatment week; and 2) GBR naive. Within these two group, animals received either ACTH+NAc DBS, ACTH+mfb DBS, ACTH, or Saline. Chronic DBS (7 days) was administered to the NAc or mfb via bilateral bipolar twisted electrodes secured to back-mounted DBS devices. Home cage activity counts were obtained for all rats using infrared beam motion detectors throughout the experiment. The open field test (OFT) was run each day of the second week, 40 minutes post-GBR and 80 minutes post-ACTH injections. Forced swim test (FST) was conducted on the last day of the protocol and animals were humanely euthanized. Total homecage activity was significantly increased in the ACTH+GBR group compared to ACTH group ($p<.01$) and other GBR groups ($p<.05$). OFT locomotor activity (day 14) was decreased in the ACTH+GBR group compared to NAc+GBR ($p<.01$) and Saline+GBR ($p<.05$) groups, but not the mfb+GBR group. FST immobility (day 15) was significantly reduced for all GBR treated animals ($p<<0.05$). NAc DBS and mfb DBS also reduced FST immobility ($p<0.05$) relative to ACTH-pretreated animals. This work confirms the therapeutic potential of NAc and mfb DBS and suggests augmentation of transient dopamine dynamics through blockade of dopamine reuptake may enhance therapeutic

outcomes. The observed increased locomotor and circadian activity underscores the pathways and mechanisms whereby this interaction might increase risk of development of a mania-like profile.

Disclosures: **R.P. Kale:** None. **A.Z. Kouzani:** None. **K. Walder:** None. **M. Berk:** Other; NHMRC Senior Principal Research Fellowship 1059660. **S.J. Tye:** None.

Poster

775. Antidepressants: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 775.09/G38

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Hypothalamic pituitary adrenal-axis hyperactivity in depression co-morbid with obesity in experimental mice

Authors: *Y. KURHE, R. MAHESH;
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Abstract: Several studies have explained the hyperactivity of hypothalamic adrenal axis in depression and obesity [1]. The present study investigates i) obesity risks the depressive behavior in mice [2] ii) corticosteroids as a pathological links for depression co-morbid with obesity [3]. Swiss albino mice were fed with high fat diet (HFD) for 14 weeks. Sucrose preference test (SPT) and forced swim test (FST) were performed in obese mice. Biochemical estimations including plasma glucose, corticosteroids and brain oxidative stress marker malonaldehyde (MDA) and anti-oxidant reduced glutathione (GSH) concentrations were performed. Results showed severe depressive behavior in HFD mice compared to normal pellet diet (NPD) fed animals as shown by reduced sucrose consumption in SPT, increased immobility time in FST (Table 1), increased plasma glucose and corticosteroids, increased brain MDA and decreased GSH (Table 2) concentration in HFD mice compared to NPD mice. The unchanged locomotor score in HFD mice compared to NPD fed mice, ruled out false positive results in FST. Present study demonstrates that obesity heightens the risk of depression in obese mice. Obesity is a stressful abnormal condition with raised oxidative stress and HPA axis hyperactivity causing abnormal corticosteroids to worsen depression by dysregulation of glucose [4]. The depressive behavior was severe in HFD mice as compared to NPD mice where HPA axis hyperactivity could play a crucial role in depression co-morbid with obesity. [1] Asensio C, et al. Int J Obes 2004;28:S45-S52. [2] Sharma S, Fulton S. Int J Obes 2012;37:382-389. [3] Lee MJ, et al. Biochim Biophys

Acta 2014;1842:473-481. [4] Matsuda M, Shimomura I. Obes Res Clin Pract 2013;7:e330-e341.

Table 1: Depressive behavior in HFD mice

Groups	Body weight (g)	Locomotor score	FST (Immobility time in sec)	SPT (% sucrose preference)
NPD control	29.83 ± 1.47	469.83 ± 15.29	136.50 ± 5.40	135.17 ± 6.51
HFD control	41.33 ± 1.63##	467.00 ± 20.02	167.67 ± 4.56##	166.83 ± 4.76##

Table 2: Estimation of biochemical parameters in HFD mice

Groups	MDA (µg/mg protein)	GSH (µg/mg protein)	Plasma glucose (mg/dl)	Plasma CORT (%)
NPD control	29.83 ± 1.47	469.83 ± 15.29	95.12 ± 7.53	100
HFD control	41.33 ± 1.63##	467.00 ± 20.02##	152.37 ± 6.14	175.62

$P < 0.01$ as compared to NPD control

Disclosures: Y. Kurhe: None. **R. Mahesh:** None.

Poster

775. Antidepressants: Animal Models

Location: Hall A

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Program#/Poster#: 775.10/G39

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: LuF Grant R166-2013-16188

Title: Disturbed inhibition in the hippocampus underlying decreased sensitivity to reward in depression

Authors: *K. HENNINGSEN[1], U. BØLCHO[2], M. M. HOLM[2], I. VIDA[3], O. WIBORG[1]; [1]Translational Neuropsychiatry Unit, Aarhus Univ., Risskov, Denmark; [2]Dept. of Biomedicine, Aarhus Univ., Aarhus, Denmark; [3]Inst. of Integrative Neuroanatomy, Berlin, Germany

Abstract: Anhedonia is defined as a decrease in sensitivity to normally rewarding stimuli. It is one of the core symptoms of depression and a common symptom in response to psychostimulant withdrawal. We have previously shown that rats with an anhedonic-like response to chronic mild stress (CMS) have an impaired hippocampal GABAergic system. This was illustrated by a decreased number of spontaneous inhibitory postsynaptic currents and an increased paired pulse facilitation in granule cells of the dentate gyrus. In this study, we have used an amphetamine withdrawal paradigm to induce an anhedonic-like condition in rats. The anhedonic-like state is measured as a decrease in sucrose consumption. In this study we aim to investigate the excitatory/inhibitory balance of rats exposed to amphetamine withdrawal using extra- and intracellular electrophysiological recording techniques. Preliminary results show that in response to amphetamine withdrawal, rats show a decrease in sucrose consumption peaking on day five, following withdrawal. Moreover, extracellular recordings indicate that amphetamine withdrawal is associated with an impaired hippocampal inhibitory system. On going studies are conducted to further delineate the functional origin of the impaired inhibition seen in our preliminary studies.

Disclosures: K. Henningsen: None. **U. Bølcho:** None. **M.M. Holm:** None. **I. Vida:** None. **O. Wiborg:** None.

Poster

775. Antidepressants: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 775.11/G40

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Wistar Kyoto rats are a model of Treatment Resistant Depression sensitive to ketamine and not fluoxetine: behavioural and molecular endpoints of pharmacological efficacy

Authors: J. PRENDERVILLE[1], J. ROUINE[1], C. MCDONNELL[1], G. DI CAPUA[1], *D. J. VIRLEY[2], M. BIANCHI[1];
[1]Transpharmation Ireland Limited, Dublin, Ireland; [2]Transpharmation Ltd, Hatfield, United Kingdom

Abstract: One third of depressed patients are unresponsive to antidepressant drugs, constituting a population known as treatment resistant depression (TRD). Ketamine is the only drug showing clinical efficacy in TRD patients. Decreased neuronal microtubule dynamics has been associated with the pathogenesis and treatment of depression and might represent a potential biomarker in TRD. The endogenous ‘depressed’ Wistar Kyoto (WKY) rat, unresponsive to selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, was used as a model of TRD to investigate

microtubular proteins as a biomarker. Male WKY rats (6-8 weeks; n=8 per group) were administered either fluoxetine (10 mg/kg i.p.), ketamine (5 mg/kg i.p.) or saline (1 ml/kg i.p.). Immobility, defined as depressive-like behaviour, was tested in the forced swimming test (FST) 30 minutes and 7 days post-administration and compared with Sprague-Dawley (SD) rats (6-8 weeks; n=8). Plasma was isolated 24 hours and 8 days post-administration; medial prefrontal cortex (mPFC) and dentate gyrus (DG) were isolated 8 days post-administration. Expression of acetylated alpha-tubulin (Acet-Tub; marker of stable microtubules) was measured as a central (brain regions) and peripheral (plasma) marker of microtubule dynamics by infrared Western Blotting. WKY rats show increased immobility in FST compared with SD rats. Ketamine produced a rapid (30 minute) and long-lasting efficacy (7 day) whereas fluoxetine elicited no effects. Plasma Acet-Tub was approx. 100% higher in WKY compared to SD rats at each time point. Importantly, fluoxetine augmented Acet-Tub overexpression in WKY rats 24 hour post-administration, ketamine had no significant effect. Neither drug significantly altered Acet-Tub expression 8 day post-administration. The observed overexpression of plasma Acet-Tub in WKY rats as well as its pharmacological modulation were similar to the alterations of microtubule dynamics identified in the brain. WKY rats represent a model of TRD responding to acute ketamine and not fluoxetine in the FST. WKY rats overexpressed plasma Acet-Tub consistent with decreased neuronal microtubule dynamics. Importantly, acute fluoxetine increased the overexpression of plasma Acet-Tub in WKY rats, an effect previously demonstrated in Lister-hooded rat hippocampus (Bianchi et al., 2009, Synapse 63:359-364), while ketamine had no effects. Thus, analysis of microtubule dynamics may represent a potential biomarker of disease progression in TRD. Transpharmation Ireland is currently analysing microtubule dynamics in plasma samples from TRD patients to explore translational and clinical relevance of its preclinical discovery.

Disclosures: **J. Prenderville:** A. Employment/Salary (full or part-time):; Transpharmation Ireland Limited. **J. Rouine:** A. Employment/Salary (full or part-time):; Transpharmation Ireland Limited. **C. McDonnell:** A. Employment/Salary (full or part-time):; Transpharmation Ireland Limited. **G. Di Capua:** A. Employment/Salary (full or part-time):; Transpharmation Ireland Limited. **D.J. Virley:** A. Employment/Salary (full or part-time):; Transpharmation Ireland Limited. **M. Bianchi:** A. Employment/Salary (full or part-time):; Transpharmation Ireland Limited.

Poster

775. Antidepressants: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 775.12/G41

Topic: C.19. Drug Discovery and Development

Title: Evaluation of antidepressant-related assays sensitive to clinical relevant doses of ketamine

Authors: *C. MOMBEREAU[1], T. BRUUN[1], J. PRENDERVILLE[3], J. ROUINE[3], L. BADOLO[2], M. BIANCHI[3];
[1]Synaptic transmission *in vivo*, [2]Discovery DMPK, H. Lundbeck A/S, Valby, Denmark;
[3]Transpharmation Ireland Limited, Dublin, Ireland

Abstract: The non-competitive NMDA antagonist ketamine has been shown to elicit a rapid and long-lasting antidepressant effects in treatment resistant depressed subjects and in preclinical models. However, discrepancies have been observed between the plasmatic concentration of clinically effective infusion and the doses routinely used in rodent limiting the translatability between these species. Indeed, both Zarate (2012) and Zhao (2012) estimated a maximal plasmatic concentration (Cmax) of 200 ng/ml after iv infusion of the sub-anesthetic dose of 0.5 mg/kg for 40 min in human whereas we estimate a Cmax of 2000-10000ng/ml after injection of the routinely used 10-30 mg/kg in rodents. This observation raise the possibility that the antidepressant-like effects of ketamine observed in preclinical models could be mediated by off-target effects such as engagement of opioids, dopamine or nicotinic receptors. In the present study, we attempt to evaluate the sensitivity of different animal models/behavioral paradigms to detect antidepressant-like effects of clinical relevant doses of ketamine such as tail suspension, forced swim test and novelty suppressed feeding test in mice and rats. Both rapid and long-lasting effects of ketamine were investigated testing the animals 30 min as well as 24h after drugs administration. Antidepressant-like effects of ketamine were observed in mice in both the tail-suspension test as well as novelty suppressed feeding at respectively 30 and 10 mg/kg with estimated plasmatic concentration of 1000-3000ng/ml. In Wistar Kyoto rats, considered as model of endogenous depression resistant to antidepressant treatment with Selective Serotonin Reuptake Inhibitors (SSRI), we observed that 3 and 5 mg/kg were able to induced fast and prolonged antidepressant like response in the forced swim test corresponding to plasmatic concentration of 100 and 200 ng/ml. Consequently, we identify the Wistar Kyoto rats as one of the most optimal model since we observed both fast and prolonged effect of ketamine at clinical relevant doses. Consequently, we will consider this model as a most appropriate entry-point in order to assess antidepressant properties of novel agent acting on NMDA receptor as well as investigate biological substrate mediating these effects. C. A. Zarate, Jr., et al., "Relationship of ketamine's plasma metabolites with response, diagnosis, and side effects in major depression," Biol. Psychiatry 72(4), 331 (2012). X. Zhao, et al., "Simultaneous population pharmacokinetic modelling of ketamine and three major metabolites in patients with treatment-resistant bipolar depression," Br. J. Clin. Pharmacol. 74(2), 304 (2012).

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Poster

775. Antidepressants: Animal Models

Location: Hall A

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Program#/Poster#: 775.13/G42

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: R01 MH086828

T32 GM008181

T32 NS063391

T32 NS007375

Title: From synapses to depression and back: plasticity of excitatory drive in cortico-mesolimbic synapses

Authors: *M. D. KVARTA[1], J. FISCHELL[2], N. HESSELGRAVE[2], T. LEGATES[2], A. VAN DYKE[2], S. THOMPSON[2];
[2]Physiol., [1]Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: A pathological weakening of excitatory synaptic transmission between multiple brain regions is induced by chronic stress and may underlie the induction of depression-related behavioral changes, such as anhedonia. Here we propose a model of multi-synaptic involvement of cortico-mesolimbic circuitry in depressive-like behavior. In this model, drive from the hippocampus (HC) and prefrontal cortex to the nucleus accumbens (NAc) is dampened by pro-depressive forces, while opposing drive from the lateral habenula is overactive, ultimately resulting in decreased dopamine release from the ventral tegmental area. Using field recordings, we show this defective circuitry contributing to anhedonia can be extrinsic to the NAc by weakening upstream synapses within CA1 of the HC following four different chronic stress models that generate a depressive-like neurobehavioral phenotype with construct, face, and predictive validity: unpredictable stress, restraint stress, multimodal stress, and exogenous CORT administration. This weakening is driven by a loss of GluA1-mediated AMPAR signaling at distal apical dendrites in the temporoammonic-CA1 (TA-CA1) pathway, and is reversed by monoaminergic antidepressant treatment. Induction of a depressive-like state characterized by anhedonia can also occur via changes intrinsic to the NAc, by weakening synapses onto NAc medium spiny neurons innervated by excitatory HC inputs. Our hypothesis predicts that restoring excitatory drive in this series of synapses will restore the normal affective state, and we show chronic administration of fluoxetine exerts this action. We predicted that negative allosteric

modulation of GABA receptors should also restore excitatory drive. Using behavioral, electrophysiological, and biochemical methods, two such compounds that target α5 subunit-containing GABA-A receptors, L-655,708 and MRK-016, promoted synchronous oscillatory activity between the HC and NAc, restored excitatory strength at TA-CA1 synapses, and restored normative behavior in social interaction and sucrose preference tests following a chronic stress paradigm, all within 24 hours of treatment. These data support an excitatory synapse hypothesis model in which depressive-like behavior is promoted by perturbing cortico-mesolimbic circuitry, and suggests novel therapeutic approaches that may be capable of rapid antidepressant effects by restoring pathologically weakened synapses within the circuit.

Disclosures: **M.D. Kvarta:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Asulon Therapeutics Inc. **J. Fischell:** None. **N. Hesselgrave:** None. **T. LeGates:** None. **A. Van Dyke:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Asulon Therapeutics Inc. **S. Thompson:** None.

Poster

775. Antidepressants: Animal Models

Location: Hall A

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Program#/Poster#: 775.14/G43

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: ISCIII-FIS Grant PI13/01102

CIBERSAM-ISCIII

Title: Effects of bacterial translocation and intestinal decontamination on the inflammatory response induced by a depression model in rats

Authors: D. MARTIN-HERNANDEZ[1,2,3], A. G. BRIS[1], K. S. MACDOWELL[1,2,3], A. SAYD[1,2,3], S. R. MAUS[1,2,3], B. GARCIA-BUENO[1,2,3], J. L. M. MADRIGAL[1,2,3], L. ALOU[1], M. L. GOMEZ-LUS[1], J. C. LEZA[1,2,3], *J. R. CASO[1,2,3];
[1]Complutense Univ. of Madrid, Madrid, Spain; [2]CIBERSAM, Madrid, Spain; [3]Inst. de Investigacion Hosp. 12 de Octubre, Madrid, Spain

Abstract: Background and purpose: there is a pressing need to identify new pharmacological targets that can result in improved tools for the treatment of the major depression disorder (MDD). Recent studies suggested that MDD is accompanied by an increased intestinal

permeability which would be related to the inflammatory pathophysiology of the disease through bacterial translocation. Thus, we aimed to evaluate if the exposure of rats to a depression model (CMS: chronic mild stress) induced an inflammatory response, both in prefrontal cortex (PFC) and colon, and to test the effects of an intestinal decontamination protocol on both structures checking the possible bacterial translocation contribution to the inflammation. Material and methods: male Wistar rats (n=8/group) were used: a control group, a CMS group and a CMS group with intestinal decontamination (CMS+ATB). Intestinal decontamination protocol was based on oral administration of antibiotics, using antibiotics without direct anti-inflammatory actions. The behavior was analyzed by means of the Forced Swim Test (FST) and the Sucrose Intake Test (SIT). The presence of bacteria in mesenteric lymph nodes (MLNs), liver, spleen and blood was evaluated as well as the LPS plasma levels. To study the possible intestinal dysfunction caused by CMS exposure, we measured mRNA or protein levels of COX-2, iNOS, IgA, CCL28, ZO-1, occludine and M1-M2 polarization factors like t-bet and STAT3. In the brain, we studied the mRNA and/or protein levels of TLR-4, phosphorylated (activated) forms of MAPK p38, ERK1/2 and JNK, dual-specificity phosphatases (DUSPs) (MKP-1, PAC-1, MKP-3) and nuclear expression of AP-1, Nrf2 and PPAR-gamma. Results: the FST and the SIT indicate a depressive-like phenotype after CMS but not in the FST for the CMS+ATB group. There is a presence of bacteria in the MLNs, liver and spleen in the CMS experimental group but not in the CMS+ATB group. The CMS induces an intestinal dysfunction that is partially restored by intestinal decontamination. In the PFC, the pro-/anti- inflammatory dysbalance detected after CMS is partially restored in the CMS+ATB group. Conclusion: our data point out to a role of the intestinal bacteria in the pathophysiology of depression at intestinal and brain levels through MAPK pathways since intestinal decontamination restore some of the CMS effects. These results are in agreement with previous data showing that external stressors to the brain, such as the LPS from bacteria, could activate innate immune receptors aggravating the stress- induced neuroinflammation and the oxidative/nitrosative damage.

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Poster

775. Antidepressants: Animal Models

Location: Hall A

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Program#/Poster#: 775.15/G44

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: Mayo-Karolinska Collaborative Grant

Title: Ketamine reduces prefrontal kynurenine levels in an animal model of treatment resistant depression

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Abstract: Ketamine is a rapid acting antidepressant, effective in a subset of patients with treatment-resistant depression. We have previously demonstrated that treatment response to ketamine is associated with elevated proinflammatory C-reactive protein levels in plasma of antidepressant resistant rats pre-treated with adrenocorticotopic hormone (ACTH). The present study aimed to extend this model through combinatorial administration of ACTH and lipopolysaccharide (LPS) and determine the relationship between ketamine response in these animals and levels of kynurenines in the prefrontal cortex (PFC). In this protocol, rats were administered ACTH (100ug/day over 14 days) and LPS (750-1250 ug/kg over three days). Rats were subjected to sucrose preference test every other day throughout the protocol, as well as open field test and forced swim test. Results demonstrate that ketamine (10mg/kg) reduced immobility during the forced swim test in rats previously injected with LPS in combination with ACTH by a mean of 78.5 seconds ($p<.0001$; $n=8$). Validity of results was corroborated by the open field test, which indicated that immobility while swimming was not due to pre-existing motor deficit. Following behavioral tests, animals were humanely euthanized and brains were frozen on dry ice. The PFC was dissected and high performance liquid chromatography was performed to examine changes in kynurenic acid and kynurenine. Levels of kynurenic acid were significantly reduced in the PFC of animals pre-treated with ACTH+LPS following ketamine administration ($p<.01$; $n=10$). However, no difference was observed between ketamine responders ($n=7$) and non-responders ($n=3$) in this effect. Similarly, levels of kynurenine were significantly reduced in the PFC of animals pre-treated with ACTH+LPS following ketamine administration ($p<.01$; $n=5$) in animals deemed ‘responders’ only. These results suggest that ketamine is an effective antidepressant in an inflammation- and chronic stress-based depression model and indicate it functionally reduces prefrontal kynurenine levels in these animals.

Disclosures: J.B. Price: None. **L. Schwieler:** None. **M. Frye:** None. **C. Sellgren:** None. **S. Erhardt:** None. **S.J. Tye:** None.

Poster

775. Antidepressants: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 775.16/H1

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: CIHR MOP 130567

CDA OG-3-14-4567-HC

HSFC 13-0002576

NSERC RGPIN-2014-06212

Title: A molecular target connecting obesity and anxiety/depression

Authors: *Z. T. QIN[1,3], X. ZHOU[3], C. CHANG[3], A. HARI[3], A. F. R. STEWART[2,4], H.-H. CHEN[1,3];
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Abstract: Emerging evidence implicates a bidirectional link between obesity and anxiety/depression. However, the mechanism remains a mystery in the diseased brain. Abnormal endocannabinoid signaling and dysfunction of hypothalamus-pituitary-adrenal axis (HPA) axis are believed to lead to obesity and depression. Inhibition of protein tyrosine phosphatase 1B (PTP1B) suppresses appetite and restores the glucose and lipid metabolism. Our study (Neuron, 2015) shows that PTP1B inhibition also attenuates stress-induced suppression of eCB signaling and anxiety. This study will focus on whether and how PTP1B-sensitive pathways are associated in this bidirectional link of obesity and depression in the HPA axis. Biochemical, electrophysiological and behavioral assessment will provide the evidence under genetic or pharmacological manipulation in the high-fat diet induced obese mice and other obese/diabetic animal models. The discoveries will suggest potential therapeutic targets to treat both metabolic and emotional disorders.

Disclosures: Z.T. Qin: None. **X. Zhou:** None. **C. Chang:** None. **A. Hari:** None. **A.F.R. Stewart:** None. **H. Chen:** None.

Poster

775. Antidepressants: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 775.17/H2

Topic: F.02. Animal Cognition and Behavior

Support: NSERC

Title: The antidepressant potential of tumor necrosis factor (TNF) alpha antagonists

Authors: *K. BRYMER, J. BOTTERILL, M. MITCHELL, H. CARUNCHO, L. KALYNCHUK;
Univ. of Saskatchewan, Saskatoon, SK, Canada

Abstract: Exposure to stressors frequently precedes the onset of depression in human patients. Accordingly, many preclinical rodent models of depression make use of chronic exposure to stress or glucocorticoids to induce a depressive phenotype. Furthermore, chronic exposure to stress promotes the release of cytokines, which in turn exacerbate the stress response and disrupt cognition. Prominent among these is the cytokine TNF-alpha, which is preferentially expressed in the hippocampus and pre-frontal cortex. We hypothesized that treating chronically-stressed rats with drugs that block the action of TNF-alpha could have antidepressant effects. In this experiment, we examined the effect of repeated corticosterone (CORT) treatment and concurrent TNF-alpha antagonism (i.e., with Enbrel) on cross-modal memory and forced-swim test (FST) behavior. Additionally, we examined object-location and object-in-place memory--tasks that are dependent on the hippocampus and pre-frontal cortex, respectively. Previous work in our lab has demonstrated that repeated CORT injections induce deficits in both object-location and object-in-place memory, however no research has examined CORT's effects on cross-modal memory. Rats received either 21 days of daily CORT injections (40 mg/kg) or vehicle injections, in addition to semi-weekly injections of Enbrel (0.8 mg/kg) or vehicle, with behavioral testing commencing on day 22. CORT increased immobility in the FST and impaired both object-location and object-in-place memory. These effects were also reversed by concurrent treatment with Enbrel. CORT also produced mild impairments in cross-modal memory, and these mild impairments were also reversed by Enbrel. These novel results show that the TNF-alpha antagonist Enbrel can have antidepressant effects in a preclinical animal model of depression. We suggest that this may occur through a restoration of function in the hippocampus and prefrontal cortex.

Disclosures: **K. Brymer:** None. **J. Botterill:** None. **M. Mitchell:** None. **H. Caruncho:** None. **L. Kalynchuk:** None.

Poster

775. Antidepressants: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 775.18/H3

Topic: A.09. Adolescent Development

Title: Ketamine modulates the dopamine system in zebrafish(danio rerio) larvae

Authors: *S. F. ALI, B. L. ROBINSON, M. DUMAS, E. CUEVAS, M. G. PAULE, J. KANUNGO;
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Abstract: Ketamine, an antagonist of the N-methyl-d-aspartate (NMDA)-type glutamate receptors, is a pediatric anesthetic. Ketamine reduces tyrosine hydroxylase (TH) levels in mammals. A number of studies show that ketamine is neurotoxic in mammals and zebrafish. In mammals, ketamine is known to modulate the dopaminergic system. Since zebrafish embryos and larvae are an ideal model system in which to assess drug toxicities, we measured the levels of dopamine (DA) and its metabolites, 3, 4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), in zebrafish larvae exposed to various doses of ketamine using HPLC/EC. Ketamine, at doses equivalent to human sub-anesthetic doses (0.1 - 0.3 mM in water), did not produce significant changes in the DA, DOPAC and HVA levels in 2-day old larvae treated for 20 h. In these larvae, TH mRNA expression remained unchanged compared to that in controls. However, 2 mM ketamine (internal exposure equivalent to the lower range of the human anesthetic dose) significantly reduced DA but not DOPAC level indicating that DA synthesis was adversely affected. Quantitative real-time polymerase chain reaction (qRT-PCR) analysis showed that, in these larvae, TH mRNA expression was significantly reduced. These results indicate that ketamine's dose-dependent effects on dopamine synthesis and TH transcription differentiate its sub-anesthetic and anesthetic doses and may be correlated with ketamine-induced neurotoxicity observed in the zebrafish early life stages.

Disclosures: S.F. Ali: None. **B.L. Robinson:** None. **M. Dumas:** None. **E. Cuevas:** None. **M.G. Paule:** None. **J. Kanungo:** None.

Poster

775. Antidepressants: Animal Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 775.19/H4

Topic: C.17. Drugs of Abuse and Addiction

Support: GM-64783

Title: Behavioral interactions between nmda receptor antagonists and antidepressants in rats

Authors: *J. A. TEMPLE, K. A. TRUJILLO, A. ROCHA, T. ZAFAR;
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Abstract: A primary pharmacological action of traditional antidepressants is to block reuptake of monoamines, however, many patients are resistant to these medications. Desipramine is a tricyclic antidepressant medication and acts by blocking norepinephrine reuptake. Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has been shown to have promising antidepressant effects in humans, including individuals resistant to currently available medications. However, because ketamine produces significant side-effects and is abused by some individuals, it is unlikely to replace traditional antidepressants. It is therefore important to better understand ketamine's antidepressant effects and develop alternatives. Past work in our laboratory, and others, has demonstrated that the combination of an NMDA receptor antagonist with a traditional antidepressant produces a profound increase in the locomotor stimulant effect of the NMDA antagonist. This suggests a strong neurochemical interaction between classical antidepressants and NMDA receptor antagonists. In the present study we examined the locomotor effects of ketamine in combination with desipramine (DMI) in Sprague Dawley rats. We hypothesized that a combination of ketamine and DMI would produce a stimulation of activity greater than either drug alone. Ketamine alone produced a short-lived stimulation of locomotor activity at both 10 mg/kg and 30 mg/kg. DMI (2.5 mg/kg) alone produced a slight locomotor depression compared to the saline control group and mildly inhibited the locomotor stimulant effect of ketamine at both doses. It is currently unclear why the combination produced effects different from those seen with other NMDA receptor antagonists, such as MK-801. We are investigating potential explanation for these unexpected results.

Disclosures: J.A. Temple: None. **K.A. Trujillo:** None. **A. Rocha:** None. **T. Zafar:** None.

Poster

776. Mood Disorders: Antidepressant III

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 776.01/H5

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: AbbVie

Title: Lack of effects of ketamine on the mTOR pathway in rats

Authors: S. POPP[1], M. M. VAN GAALEN[2], A. BESPALOV[1], *B. BEHL[1];
[1]AbbVie Deutschland GmbH & Co.KG, Ludwigshafen, Germany; [2]Encepharm, Goettingen, Germany

Abstract: A single dose of ketamine produces a robust antidepressant response within hours after infusion that lasts for a week or even longer in some patients. Recently, Li et al. (Science, 239: 959-64, 2010) suggested that the rapid antidepressant effects of ketamine are mediated by activation of the mTOR pathway associated with a rapid and sustained elevation of synapse-associated proteins and spine numbers in the prefrontal cortex (PFC). We attempted to reproduce these results following the methods described in the Li paper. We subjected male Sprague-Dawley rats to a forced swim test and assessed the effects of ketamine on both the mTor pathway and the latency to immobility as a measure of antidepressant-like effects. After a single i.p. application of 10 or 30 mg/kg, ketamine did not influence levels of phosphorylated forms of mTOR, p70S6K and S6 ribosomal protein in the prefrontal cortex (1 h post-injection) or synaptic proteins (Synapsin I, PSD95 and GluR1), the translation of which is controlled by the mTOR pathway (3 h post-injection). Meanwhile, ketamine produced a dose-dependent increase in latency to immobility in the rat forced swim test, an effect that could be dissociated from the ability of ketamine to enhance locomotor activity in the open field. To further validate the protocols used to assess changes in the mTor pathway, we demonstrated that rapamycin (10 or 25 mg/kg i.p.) administered for 8 days strongly inhibited the phosphorylation of the S6 ribosomal protein. Thus, despite using the protocol maximally close to that described by Li et al. as well as trying multiple variations of this protocol we were unable to reproduce previously published activation of the mTOR pathway by ketamine. *Disclosures: All authors are/were employees of AbbVie. The design, study conduct, and financial support for this research was provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the publication.*

Disclosures: **S. Popp:** A. Employment/Salary (full or part-time):; AbbVie. **M.M. van Gaalen:** A. Employment/Salary (full or part-time):; Encepharm. **A. Bespalov:** A. Employment/Salary (full or part-time):; AbbVie. **B. Behl:** A. Employment/Salary (full or part-time):; AbbVie.

Poster

776. Mood Disorders: Antidepressant III

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 776.02/H6

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Different classes of antidepressants produce divergent effects in the open space swimming test in the mouse

Authors: *V. CASTAGNÉ, C. LANDEMAINE, V. LÉON;
Porsolt S.A.S., Le Genest-saint-Isle, France

Abstract: The open space swimming test (OSST) is considered a potential model for the assessment of chronic treatment with antidepressants and it is based on the use of repeated sessions of forced swimming. During the OSST, mice progressively develop a passive behavior (observed as low distance swum and long duration of immobility), which stabilizes with the repetition of swimming sessions. The present study evaluated the effects of different classes of antidepressants in the OSST. Male NMRI mice were submitted to 15-minutes swimming sessions during which their behavior was video recorded. The distance swum and the time spent immobile were analyzed by video-tracking during test sessions. Swimming sessions were performed daily from Day 1 to Day 5 in order to induce a stable passive behavior in animals before any pharmacological treatment. Thereafter, swimming sessions were performed at 3 or 4 days intervals. Daily intraperitoneal treatments were administered starting on Day 8 and continued until the end of the experiments. During the first swimming sessions, mice progressively developed a passive behavior, as reflected in shorter distance swum and a longer duration of immobility on Day 5, as compared with Day 1. Thereafter, passive behavior remains stable in vehicle control mice. Antidepressants acting mainly on norepinephrine (NE) neurotransmission such as imipramine or desipramine reverse this passive behavior. In particular, imipramine (30 mg/kg i.p.) clearly increases the distance swum and decreases the duration of immobility ($p < 0.001$ on all testing days). In contrast, Serotonin Selective Reuptake Inhibitors (SSRIs) such as fluoxetine and escitalopram, aggravate the passivity of the animals. Several experiments confirmed these observations after both acute and chronic treatment with the different classes of substances. Finally, mice initially treated with escitalopram for a period of 2 weeks and then treated with desipramine for an equivalent period display a biphasic change in passive behavior (an increase induced by escitalopram followed by a decrease in passivity induced by desipramine, as compared with vehicle controls). The OSST and the forced swimming test (FST) therefore seem able to detect opposite effects of different classes of antidepressants in the mouse. Our data suggest that the repeated but predictable swimming stress during OSST induces a passive behavior which can be either reversed or further accentuated by substances increasing NE or 5-HT neurotransmission, respectively. In contrast, all classes of antidepressants tend to reverse the passive behavior induced by the acute but non-controllable swimming stress in the FST.

Disclosures: V. Castagné: A. Employment/Salary (full or part-time):; Porsolt SAS. **C. Landemaine:** None. **V. Léon:** None.

Poster

776. Mood Disorders: Antidepressant III

Location: Hall A

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Program#/Poster#: 776.03/H7

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: NIH R01-MH087583

NIH R01-MH099085

Title: Sex differences in the abuse potential of low-dose ketamine

Authors: *K. J. SCHOEPFER[1], C. E. STRONG[1], S. K. SALAND[1], A. M. DOSSAT[1], F. JOHNSON[2], M. KABBAJ[1];
[1]Dept. of Biomed. Sci., [2]Dept. of Psychology, Florida State Univ., Tallahassee, FL

Abstract: In clinical studies, low subanesthetic doses of the noncompetitive NMDA receptor antagonist ketamine (KET) have been shown to produce rapid (within hours) and long-lasting (up to 2 weeks) antidepressant effects in treatment-resistant patients. Interestingly, more recent clinical studies have demonstrated that the antidepressant effects of ketamine can be maintained over much longer periods of time if the drug is administered repeatedly. This may be problematic because ketamine in high doses is known to have addictive properties and is recreationally abused. Therefore, more studies delving into the safety of repeated infusions of low doses of ketamine are warranted. We have recently reported that female rats are more sensitive than males to KET's antidepressant-like effects, responding to 2.5 and 5.0 mg/kg (i.p.), respectively, and therefore aimed to determine whether there are also sex differences in the addictive properties of repeated low-dose KET treatment. We thus assessed the rewarding properties of repeated low-dose KET (0, 2.5, or 5.0 mg/kg, i.p.) in adult male and female Sprague-Dawley rats. We found that regardless of sex, dose, or treatment frequency, rats did not develop a conditioned place preference for low-dose KET, suggesting repeated KET treatment at therapeutically-relevant doses is not rewarding. We also assessed behavioral sensitization to the locomotor-activating effects of KET. We found that both male and female rats sensitized, and that their responses at 2.5 and 5 mg/kg KET depended on the frequency (every other day vs. weekly) of treatment injections. The behavioral outcomes of the sensitization experiments in both sexes were consistent with changes in the expression of markers of synaptic plasticity and dendritic spine densities in the nucleus accumbens. Taken together, these findings suggest that repeated low-dose KET treatments can induce behavioral and physiological changes similar to changes induced by other drugs of abuse and high doses of ketamine. Therefore, more studies like this are

warranted to determine the safety of repeated low-dose KET treatment for treatment-resistant depression.

Disclosures: K.J. Schoepfer: None. **C.E. Strong:** None. **S.K. Saland:** None. **A.M. Dossat:** None. **F. Johnson:** None. **M. Kabbaj:** None.

Poster

776. Mood Disorders: Antidepressant III

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 776.04/H8

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Antidepressant activity of rose oil in Wistar Kyoto rats

Authors: *K. LOK, S.-T. LI;
Bio-X Inst., Shanghai Jiao Tong Univ., Shanghai, China

Abstract: Objective: Depression is one of the most common psychiatric disorder that results in significant consequences in many countries. Clinicians managing depressed patients face two challenges: First, some antidepressants' therapies are associated with a variety of side effects. Second, longer time are needed for some antidepressants to work effectively. Such consequences cause medication non-adherence and discontinuation. In traditional manuscripts there are many indications about the anxiolytic effects of rose oil, and toxicity rarely occurs with appropriate use of essential oils. So far, however, less scientific research have been done about antidepressant effect of essential oil, even though this is one of the most commonly used aromatherapy. The purpose of present study was to determine the effects on depression like behaviors and underlying mechanisms of inhaled rose essential oil. **Methods:** All experiments were carried out on 6 weeks old male Wistar Kyoto (WKY) rats. Rats were allowed to inhale rose essential oil's-, or its principal constituent β-Citronellol oil's vapors for 2 weeks (7 hours/day) in a special cage prior to performing the behavioral tests. Control animals were caged in the same conditions but in the absence of the tested oils. Locomotor activity of animals were measured by total distance travelled in open field test (OFT). The antidepressant activities of rose oil and β-Citronellol were assessed using the forced swim test (FST). Proteomic analysis using an isobaric tag for relative and absolute quantitation (iTRAQ) and tandem mass spectrometry was performed to identify differentially expressed proteins in the hippocampus of different groups. Then, some of the depression-related proteins were followed-up simultaneously in qRT-PCR, western blot, and immunohistochemistry assays. **Results:** No significant alterations of locomotor activity in OFT were detected in oil-inhaled WKY rats. While significantly reduced immobile time (I.T) in FST

were observed in WKY rats after rose- or β-Citronellol oil-treatments. Using the iTRAQ-approach, 26 differentially regulated proteins were identified in β-Citronellol treated WKY rats. We further analyzed the changes of protein expression levels by western blotting and immunohistochemistry methods. **Conclusion:** The results showed that inhalation of rose or β-Citronellol essential oils possess antidepressant-like effects, suggesting that it is a simple, low-risk, and cost effective interventions of depression.

Disclosures: K. Lok: None. **S. Li:** None.

Poster

776. Mood Disorders: Antidepressant III

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: Mnemosyne Pharmaceuticals Inc.

Title: Potential neurophysiological signals tracing antidepressant effects of glutamate receptor antagonists

Authors: *D. NAGY[1], M. STOILJKOVIC[1], F. MENNITI[2], M. HAJOS[1];
[1]Yale Univ., New Haven, CT; [2]Mnemosyne Pharmaceuticals Inc., Providence, RI

Abstract: Ketamine is a non-competitive NMDA receptor channel blocker with rapid onset antidepressant effects. Clinical observations in depressed patients responding to ketamine suggests that efficacy results from synaptic potentiation, indexed as an increase in sensory evoked potentials, after the drug is eliminated (Cornwell et al., 2012). However, ketamine also causes a psychotomimetic response tightly linked to drug exposure. An open question is the mechanistic relationship between the 'Drug-On' psychotomimetic and 'Drug-Off' antidepressant effects. To investigate this, we compared Drug-On and Drug-Off effects of ketamine with an NR2B-selective NMDA antagonist, CP-101,606, that also has rapid onset antidepressant efficacy. Aims were 1) model ketamine-induced, Drug-Off increases in sensory evoked potentials, 2) determine whether CP-101,606 had similar effect, and 3) compare the Drug-On effects to gain insight into which of these may account for the Drug-Off effects. The effects of ketamine (5, 10 and 80 mg/kg) and CP-101,606 (2, 6.7 and 20 mg/kg, sc) were determined on auditory evoked potentials (AEPs), auditory gating and local field potentials in hippocampal CA3 and primary auditory cortex in freely-moving rats. Neurophysiological responses were analyzed at 5-30 min when drug exposures were maximal (Drug-On) and 5-6 hours, after drugs

were eliminated (Drug-Off). Ketamine Drug-On dose-dependently disrupted auditory gating and increased delta and gamma band power, and at the high dose reduced AEP amplitude in the hippocampus and cortex. Effects were attenuated or absent in Drug-Off phase. Importantly, the predicted antidepressant dose of ketamine (10 mg/kg, sc) significantly enhanced AEPs in cortex and hippocampus in the Drug-Off phase. Similar to ketamine, CP-101,606 significantly enhanced AEPs in cortex and hippocampus in Drug-Off period. However, CP-101,606 Drug-On did not disrupt auditory gating or alter gamma or delta oscillations. Our findings show that both ketamine and CP-101,606 augment AEPs during Drug-Off phase, consistent with a possible mechanism for antidepressant efficacy. CP-101,606 was distinctively different from ketamine during Drug-On phase since it did not disrupt auditory gating or alter gamma and delta oscillations. Thus, antidepressant efficacy of NMDA receptor inhibition may arise from a mechanism distinct from that causing the Drug-On effects of ketamine, which may be linked to psychotomimetic effects. Furthermore, sensory evoked potentials may serve as potential translational biomarkers of antidepressant efficacy applicable to developing drugs targeting glutamatergic neurotransmission.

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Poster

776. Mood Disorders: Antidepressant III

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 776.06/H10

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Comparison of variables associated with postpartum depression in adolescent and adult women with low socioeconomic status in the southeast of Mexico

Authors: *H. A. RUBIO-ZAPATA[1], D. F. ESTRELLA-CASTILLO[2], P. AGUILAR-ALONSO[3], K. B. OJEDA-TORRES[4];
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Abstract: Postpartum depression (PPD) is a pathological mood disorder that usually occurs between the first 6-8 weeks after birth, it is common to confuse the emotional disorders of pregnancy, so diagnosis may be overlooked. However diminishes the quality of life of the patient and affects the health of mother and child. Its origin is multifactorial so its incidence and prevalence vary widely. Low socioeconomic status has been reported as a risk factor for presenting PPD, which is why the objective of this study was to compare the epidemiological characteristics of adult and adolescent women with PPD treated at a public hospital for poor people in Mexico Yucatan. A comparative study involving 110 adult women and 110 adolescents randomly selected, attended by vaginal delivery in the maternity hospital in Merida, Yucatan, during July and August 2014. All participants answered the Spanish Version of the Scale Edinburgh Postnatal Depression, an epidemiological questionnaire and AMAI scale to determine socioeconomic status. No patients with difficult births or cesarean sections, or with known mental illness or treated with psychotropic drugs were included. Results: The age of adult women was 25.35 ± 4.84 years and 17.6 ± 9.9 in adolescent. The frequency of postpartum depression in adults was 21%, while in adolescents was 13%. The average value of the scale of Edinburgh was 13.19 ± 0.6 for adults and 13.77 ± 1.6 for adolescents with PPD (t-Student p = 0.67). The associations significant with DPP were: adult (chi2, p = 0.027), unemployed and adult (p = 0.001), physical abuse and adult (p= 0.02) and single-teen (P = 0.004), there was no association with the other variables: schooling, sexual abuse, parity, contraceptive use, unwanted pregnancy, unplanned pregnancy, number of sexual partners, product weight, and others. In conclusion adult women had higher frequency of PPD than adolescents. The PPD was associated with abuse, unemployment, and being single. The factors associated with PPD were different between adults and adolescents with low socioeconomic status in the southeast of Mexico

Disclosures: H.A. Rubio-Zapata: None. **D.F. Estrella-Castillo:** None. **P. Aguilar-Alonso:** None. **K.B. Ojeda-Torres:** None.

Poster

776. Mood Disorders: Antidepressant III

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Program#/Poster#: 776.07/H11

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: JSPS KAKENHI 26860951

JSPS KAKENHI 24791244

Title: Chronic treatment with antidepressants enhances dopamine D1 receptor signaling in the hippocampal dentate gyrus

Authors: *M. KUROIWA[1], T. SHUTO[1], N. SOTOGAKU[1], Y.-S. OH[2], A. NISHI[1];
[1]Kurume Univ. Sch. of Med., Kurume, Fukuoka, Japan; [2]the Rockefeller Univ., New York, NY

Abstract: Major depression is a psychiatric disorder with high lifetime prevalence. Antidepressants have been widely used to treat major depression, although the mechanisms underlying their therapeutic effects are not fully understood. Hippocampal dentate gyrus (DG) is one of target brain regions for antidepressants. Recently, chronic treatment with a selective serotonin reuptake inhibitor, fluoxetine, is reported to induce functional changes of mature granule cells in the hippocampal dentate gyrus, in addition to the facilitation of adult neurogenesis. The mature granule cells affected by chronic fluoxetine treatment show a decrease in expression of calbindin, a marker of mature granule cells, and an increase in expression of dopamine D1 receptors (Kobayashi et al., 2010). In this study, we investigated the expression profile and function of dopamine D1 receptors in the dentate gyrus after chronic antidepressant treatment. Treatment of mice with fluoxetine (15 mg/kg/day) for 14 days increased the expression of D1 receptors, but not other subtypes of dopamine receptors, in mRNA and protein levels only in the DG. Immunohistochemical analysis in Drd1a-EGFP mice revealed that the expression of D1 receptors is mainly induced in NeuN and calbindin-positive granule cells. The ability of a D1 receptor agonist, SKF81297, to phosphorylate DARPP-32 at Thr34 (PKA-site) in DG slices was enhanced in fluoxetine-treated mice. These results suggest that chronic treatment with fluoxetine induces the up-regulation of D1 receptor signaling in the DG, which may contribute to therapeutic action of antidepressants.

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Poster

776. Mood Disorders: Antidepressant III

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Program#/Poster#: 776.08/H12

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Effect of the antidepressant agomelatine on the inflammatory response induced by lipopolysaccharide: a genome-wide study in the rat ventral hippocampus

Authors: A. C. ROSSETTI[1], M. S. PALADINI[1], G. RACAGNI[1], M. A. RIVA[1], A. CATTANEO[2,3], *R. MOLTENI[1];
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Abstract: Growing evidence suggests that the activation of the immune/inflammatory system may be associated with depression pathogenesis and, in line with this observation, several studies mainly focused on pro-inflammatory cytokines reported that antidepressant drugs have immunoregulatory effects. However, given the complexity of the inflammatory response, which implies the integration of different mechanisms triggered by various systems, the aim of the present work was to assess the anti-inflammatory properties of the antidepressant agomelatine with an unbiased genome-wide approach by using the microarray technique. Specifically, we analysed the gene expression profile of the ventral hippocampus, a cerebral area relevant for depression, of adult rats chronically treated with the antidepressant before to receive a systemic injection of lipopolysaccharide (LPS) in comparison with animals treated with saline. To this aim, adult male Sprague-Dawley rats received agomelatine or vehicle for 21 days before being challenged with an acute injection of LPS or saline 16 h after the last drug administration. Animals were sacrificed 2 h after the immune challenge and the ventral hippocampus was dissected and processed for RNA extraction. Transcriptomic analysis was performed using Affymetrix® Array and the results were analyzed with Partek Genomics Suite and with Ingenuity Pathway Analyses software. We found that LPS administration induced the transcription of 284 genes mainly associated with pathways related to inflammation. Conversely, chronic treatment with agomelatine alone modulated 105 transcripts belonging to different pathways in saline-treated rats, like the phospolipase C and the CXCR4 pathways. Moreover, the drug was able to prevent the LPS-induced modulation of 91 genes with respect to the control group and of 52 genes with respect to animals treated only with LPS. An intersection analysis between these two lists of genes led to the identification of some transcripts induced by LPS on which agomelatine has the larger effect of normalization. In summary, by using a genome-wide approach, we have highlighted the transcriptional profile of a chronic treatment with agomelatine both at basal state -identifying genes and pathways related to the basal effects of the antidepressant- and in condition of acute inflammation - identifying genes and pathways associated to its anti-inflammatory properties. These genes/pathways might represent potential new targets for pharmacological intervention of depression associated to inflammation.

Disclosures: **A.C. Rossetti:** None. **M.S. Paladini:** None. **G. Racagni:** D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Servier, Janssen, Otsuka. **M.A. Riva:** D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Servier, Eli Lilly, Lundbeck, Sumitomo Dainippom Pharma Co. Ltd and Sunovion. **A. Cattaneo:** None. **R. Molteni:** None.

Poster

776. Mood Disorders: Antidepressant III

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 776.09/H13

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: Lundbeck Research USA, Inc.

Title: Impact of vortioxetine on spontaneous and afferent-driven spike activity recorded in the rat ventral striatum/nucleus accumbens

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Abstract: The novel antidepressant vortioxetine is currently used in the clinic to treat major depressive disorder. In addition to blocking serotonin (5-HT) reuptake via inhibition of the 5-HT transporter (SERT), vortioxetine is a $5HT_{1A}$ receptor agonist, $5HT_{1B}$ receptor partial agonist, and an antagonist at the $5HT_{1D}$, $5HT_3$, and $5HT_7$ receptors. Vortioxetine has been shown to enhance 5-HT transmission in the prefrontal cortex (PFC) and can potentially affect 5-HT signaling in other brain regions, such as the ventral striatum/nucleus accumbens (VS/NAc) which also play key roles in the control of motivated behaviors. Thus, the current study utilized both between- and within-subjects designs to examine the impact of systemic vortioxetine (0.8 mg/kg, i.v.) administration on spontaneous and PFC-evoked spike activity of electrophysiologically identified VS/NAc medium-sized spiny projection neurons (MSNs) recorded in urethane-anesthetized rats. In between-subjects studies, following vortioxetine administration (10-60 min), VS/NAc MSNs exhibited decreases in both the probability and onset latency of PFC-evoked spikes. No significant effects of vortioxetine on spontaneous firing activity were apparent. The vortioxetine-induced decrease in the onset latency of PFC-evoked spikes was also replicated in within-subjects studies in which MSNs were recorded prior to, and up to 40 minutes after, drug administration. Vortioxetine administration also induced a substantial decrease (>50%) in the magnitude of PFC-evoked spike activity observed following train stimulation of the hippocampal

fimbria as compared to pre-drug controls. Taken together, the current studies indicate that vortioxetine is likely to exert complex modulatory effects on prefrontal corticoaccumbens pathways and the responsiveness of VS/NAc MSNs to excitatory inputs from the hippocampal fimbria. Future studies assessing the impact of this multimodal serotonergic compound on PFC neuron activity and local feed-forward inhibitory processes in prefrontal corticoaccumbens pathways may reveal novel strategies for treating disorders of motivated behavior.

Disclosures: S. Chakroborty: None. **E. Dale:** None. **A.L. Pehrson:** None. **C. Sanchez-Morillo:** None. **A.R. West:** None.

Poster

776. Mood Disorders: Antidepressant III

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: FIS PI12/00613

IT747-13

UFI 11/32

PI12/00915

P11-CTS-07748

Title: Ketamine promotes electrophysiological and biochemical alterations in the glutamatergic transmission in the dorsal raphe

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Abstract: Evidence demonstrates that administration of glutamatergic antagonists, and particularly ketamine, exert rapid antidepressant effects. The tight interactions between glutamatergic and monoaminergic systems and the shared actions between the classical and the novel antidepressants have been well-described. This gives rise to the possibility that ketamine

could exert its antidepressant effects by acting on monoaminergic areas, such as the dorsal raphe (DR). Here, we used electrophysiological and biochemical approaches to determine whether ketamine is altering the glutamatergic transmission and the mTOR pathway in the DR, besides promoting rapid antidepressant-like behaviors. In the tail suspension test we replicated the preclinical findings showing that ketamine (30 mg/kg, i.p.) has acute (30 min) and sustained (24h) antidepressant-like effects in mice. By using whole-cell patch-clamp recordings we observed that bath perfusion of ketamine (50 μM, 10 min) increased the frequency of sEPSCs in DR neurons. In addition, the AMPA receptor antagonist 6,7-dinitroquinoxaline-2,3-dione (DNQX, 10 μM) blocked this effect, and the NMDA receptor antagonist D-2-amino-5-phosphonopentanoate (D-AP5, 50 μM) failed to increase the frequency of sEPSC, showing that the observed ketamine-induced glutamate release involves AMPA, but not NMDA receptors. Furthermore, pre-incubation of the slices with the mTOR inhibitor PP242 (2.5 μM, 40 min) attenuated the effect of ketamine on sEPSC. However, when ketamine was administered 24 hours prior to the recordings, it produced no effects either in sEPSCs or eEPSCs, pointing out a functional difference between the acute and sustained effects of this drug in the DR. Finally, western blot experiments revealed that ketamine (30 mg/kg, i.p.) did not induce acute (30 min) phosphorylation of mTOR in the DR, whereas 24 hours after the injection ketamine increased the levels of the phosphorylated-active form of mTOR. Collectively, these results identify functional actions of ketamine on the glutamatergic transmission in the DR, and also reveal that the AMPA receptor-mediated electrophysiological “rapid onset” effects, which may trigger other functional/cellular effects, are not maintained in the DR 24 hours after the administration of ketamine.

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Poster

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: TIFR intramural grant

Title: Age-dependent effects of chronic electroconvulsive seizure (ECS) treatment

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Abstract: Electroconvulsive seizure (ECS) treatment is a fast-acting antidepressant treatment that is often the therapy of choice for depressed patients refractory to pharmacological antidepressants, as well as in cases of geriatric depression. While preclinical studies with ECS have identified several molecular, cellular and behavioral changes that arise following repeated seizure treatments, the underlying mechanisms of action for this treatment modality remain poorly understood. In animal models, ECS evokes a robust activation of several immediate early and plasticity-associated genes, enhances monoamine turnover, increases hippocampal neurogenesis, evokes axonal sprouting and dendritic reorganization, accompanied by robust effects on mood-related behavioral tasks. However, thus far the preclinical studies have been performed in young animals and have been presumed to evoke a similar constellation of changes as animals age into middle-aged life. The primary focus of our study was to examine the age-dependent effects of ECS by comparing the molecular, neurogenic, structural and behavioral effects evoked by ECS in young (2 month) and middle-aged (12 month) adult male Sprague-Dawley rats. Behavioral studies revealed that ECS evoked antidepressant-like behavioral responses on the Forced Swim Test in both young and middle-aged animals. Molecular studies profiling gene expression in the hippocampus thus far indicate that while regulation of trophic factors (bdnf, vegfa, fgf2) and immediate-early gene (arc, c-fos, egr-1-3) expression did not differ significantly in either the nature or the extent of regulation at the two ages examined, genes associated with the formation of perineuronal nets were differentially regulated by ECS in an age-dependent manner. Specifically, the expression of ncan, vcan, hapln1 and has2 were shown to be increased by ECS in middle-aged, but not in young adult animals. Interestingly, detailed gene expression analysis of autophagy associated genes (lc3a, becn1, atg4b, ulk1) showed a significant decrease in young adults, but not in middle-aged animals. Studies are currently underway to characterize age-dependent effects of ECS on neurogenesis, gene expression, perineuronal net architecture, cell death, mitochondrial function and signaling pathways. Our results suggest that the molecular and cellular effects of ECS on the hippocampus are age-dependent. This raises the intriguing possibility that distinct temporally dependent consequences may underlie the behavioral effects of ECS at the time points studied.

Disclosures: **M. Jaggar:** None. **S. Ghosh:** None. **V.A. Vaidya:** None.

Poster

776. Mood Disorders: Antidepressant III

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: R01-MH087583

R01-MH099085

Title: Sex differences in the reinforcing properties of intermittent, low-dose ketamine

Authors: *K. N. WRIGHT, C. E. STRONG, M. KABBAJ;
Biomed. Sci., Florida State Univ., Tallahassee, FL

Abstract: Major depressive disorder (MDD) is a chronic debilitating disease that affects twice as many women as men. While antidepressants such as fluoxetine are only effective in a portion of patients, the N-methyl-d-aspartate (NMDA) receptor antagonist ketamine can rapidly reduce depressive symptoms in most treatment-resistant individuals for MDD as well as bipolar disorder, with multiple infusions prolonging the effect. Although ketamine has therapeutic value, chronic exposure to higher doses has well-documented abuse potential and detrimental health effects. Low-dose ketamine's abuse potential has not been thoroughly assessed, a growing concern especially for women who are not only more vulnerable to developing addiction than men, but also have higher comorbidity for drug addiction and MDD. Therefore in this study, we aimed to assess whether low doses of ketamine are reinforcing and whether there are sex differences in its reinforcing properties. To do this, we utilized intravenous self-administration (100 μg/kg/infusion, with 50 maximum infusions) in male and female rats. Intact cycling females self-administered ketamine only on days when they were in proestrus (when gonadal hormones are high) or diestrus (when hormones are low, determined by daily vaginal lavage), and males self-administered ketamine once every four days. This timeframe was used to mimic clinically relevant administration and to determine how cycling E2 and P4 influence the response to ketamine in females. Male rats maintain stable self-administration of this low dose on FR1, and we are currently investigating their behavior on FR2, FR5, and progressive ratio schedules of reinforcement. Rats will also undergo extinction followed by cue-induced and drug-primed reinstatement to determine if males and females are vulnerable to relapse, a major hurdle on the path to recovery from addiction. Additionally, since there is evidence of hormonal modulation of intracellular signaling in the reward pathway with psychostimulants, we will determine whether there are sex differences in the expression of molecular targets in the nucleus accumbens that are altered by ketamine self-administration. These markers include brain-derived neurotropic factor (BDNF), glycogen synthase kinase-3 (GSK-3), and delta FosB (ΔFosB). Taken together, this study helps to characterize the safety of low-dose repeated ketamine for the treatment of MDD.

Disclosures: K.N. Wright: None. **C.E. Strong:** None. **M. Kabbaj:** None.

Poster

776. Mood Disorders: Antidepressant III

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Hippocampal neurogenesis is required for some of the antidepressant- and anxiolytic-like properties of S 47445, a novel positive allosteric modulator of AMPA type glutamate receptors

Authors: J.-P. J. P. GUILLOUX[1], I. MENDEZ-DAVID[1], A. GARDIER[1], L. TRITSCHLER[1], E. MOCAER[2], *S. BRETIN[2], D. DAVID[1];
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Abstract: S 47445 is a potentiator of glutamate AMPA receptors possessing procognitive, neurotrophic properties and enhancing synaptic plasticity 1,2). Here, the anxiolytic/antidepressant-like effects of S 47445 were investigated in a mouse model of anxiety/depression based on chronic corticosterone administration. The contribution of hippocampal neurogenesis in these effects was also studied. Four doses of S 47445 (0.3-1-3-10mg/kg, per os, for 4 weeks) were assessed on different anxiety- and depression-related behaviors (the elevated plus maze (EPM), open field (OF), splash test (ST), forced swim test (FST), tail suspension test (TST) and fur coat state) as well as on hippocampal neurogenesis in comparison with chronic fluoxetine treatment (18 mg/kg/day, per os, for 4 weeks), a serotonergic antidepressant. Then, the anxiety/depression model was combined with a genetic ablation of hippocampal neurogenesis (GFAP-Tk model) and the neurogenesis dependence of the behavioural effects of chronic treatment with 10mg/kg of S 47445 was studied and Brain Derived Neurotrophic Factor levels were also measured in hippocampus. S 47445 at 3 and 10mg/kg reversed corticosterone-induced depressive-like state by increasing grooming duration and decreasing the immobility duration in TST and FST, respectively. The coat state's deterioration was reversed at all tested doses. Moreover, S 47445 significantly reversed the anxiety phenotype observed in OF and EPM, at 1mg/kg and at 1, 3, 10mg/kg, respectively. Significant effects were observed with fluoxetine for all these tests, excepted for the coat state in which it was inefficient. S 47445 also demonstrated significant neurogenic effects on proliferation, survival and maturation of hippocampal newborn neurons mainly at 3 and 10mg/kg. Interestingly, at these 2 doses, it significantly corrected corticosterone-induced deficits of dendrites arborisation by increasing both dendritic lengths and number of intersections. Finally, S 47445 had anxiolytic/antidepressant-like activity specifically in the novelty suppressed feeding test requiring adult hippocampal neurogenesis. The increase in hippocampal mature BDNF levels observed at 10mg/kg is one of the mechanisms of S 47445 mediating the adult hippocampal neurogenesis's increase. Altogether, the AMPA potentiator S 47445 displays robust antidepressant-anxiolytic-like properties after chronic administration through neurogenesis dependent/independent mechanisms and neuroplastic activities. S 47445 could have promising

therapeutic potential for the treatment of major depressive disorders or generalized anxiety disorders.

Disclosures: J.J.P. Guilloux: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Institut de Recherches Internationales Servier. **I. Mendez-David:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Institut de Recherches Internationales Servier. **A. Gardier:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Institut de Recherches Internationales Servier. **L. Tritschler:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Institut de Recherches Internationales Servier. **E. Mocaer:** None. **S. Bretin:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Institut de Recherches Internationales Servier. **D. David:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Institut de Recherches Internationales Servier.

Poster

776. Mood Disorders: Antidepressant III

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Program#/Poster#: 776.14/H18

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: IOER Funds

Title: Combinational antidepressant effects of glutamatergic agents

Authors: J. KLINE, K. BATTANI, *L. SEMKE, V. DURIC, L.-L. YUAN;
Physiol. and Pharmacol., Des Moines Univ., Des Moines, IA

Abstract: Accumulating evidence suggests dysregulation of glutamatergic transmission in the brain is linked with depressive disorders. Ketamine, an antagonist of a subtype of glutamate receptors, exhibits fast-acting and long-lasting antidepressant effects in humans and in animal models. However, limitations of ketamine use as a long-term treatment, particularly its dissociative/psychotomimetic effects and abuse potential, highlight the need for alternative glutamatergic agents. D-serine, an endogenous NMDA receptor co-agonist, also targets glutamate transmission and has shown therapeutic potential in preclinical models of depression. Their opposing actions on the shared target (NMDAR) and the highly overlapped molecular signature evoked by ketamine and D-serine raises the possibility that their co-administration may diminishes adverse side effects of ketamine without compromising its antidepressant effectiveness. Immediately following intraperitoneal injection (< 1 min), ketamine (10 mg/kg) altered states of consciousness and induces motor incoordination in mice. Co-administration of D-serine significantly reduced the level of motor incoordination as quantified by the number of falls induced by ketamine. However, the antidepressant effects of ketamine did not appear to be compromised by D-serine as assessed in the forced swim test. In parallel with its behavioral influences, D-serine addition did not interfere with ketamine-activated signaling pathways at the 1-hour post injection time point; it actually enhanced ketamine's effects on key synaptic proteins at the 24-hour time point. These results support the notion that ketamine and D-serine may represent a more effective combination therapy than either one alone.

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Poster

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Portuguese Foundation for Science and Technology (FCT)

Title: Cell cycle regulation of the adult hippocampal progenitor cells in depression and by antidepressants

Authors: *P. PATRICIO, A. MATEUS-PINHEIRO, A. MACHADO-SANTOS, N. ALVES, M. MORAIS, J. BESSA, N. SOUSA, L. PINTO;
Life and Hlth. Sci. Res. Inst. (ICVS), Braga, Portugal

Abstract: Depression is a complex and multidimensional disorder affecting around 20% of the world population. Alterations in hippocampal dendritic morphology and cell proliferation/genesis are known to be involved in the pathophysiology of depression and in the actions of antidepressants (ADs). Indeed, decreased cell genesis and dendritic atrophy were detected in the hippocampus of depressed individuals, whereas ADs treatment prevented it. Previous genome-wide studies by our group disclosed differential molecular regulation by different classes of ADs in the hippocampal dentate gyrus (hDG) of the uCMS (unpredictable chronic mild stress) rat model of depression (Patrício et al., Neuropsychopharmacology, 2015). Following this study, the cell cycle mechanisms regulating hippocampal cell proliferation and cell genesis were investigated using *in vivo* (macrodissected hDG) and *in vitro* (rat hippocampal-derived neurospheres; NSP) approaches. UCMS animals presented a slight increase in the percentage of cells in G1 phase of the cell cycle. Accordingly, these cells had decreased expression levels of cyclin D1 compared to controls, whereas fluoxetine-treated animals reversed these levels to those of controls. To better characterize these responses, we used an NSP culture. This system allowed enriching our population in hippocampal-derived progenitor cells. Dexamethasone (DEX; glucocorticoid (GC) receptor agonist; 1 μM) and corticosterone (CORT; hormone that activates both GCs and mineralocorticoid receptors; 1 μM) were applied to the NSP for 6 days, to mimic the effects of GCs elevation in the brains of depressed individuals and animal models of depression. Moreover, neurotransmitters involved in the action of monoaminergic ADs (norepinephrine and serotonin) were applied to the DEX/CORT-treated cells, in the last 4 days of culturing. PI staining was used for cell cycle distribution assessment by flow cytometry. A G1 phase arrest was detected in the DEX-treated cells. Addition of neurotransmitters to the cells partly reversed this arrest. The expression of G1 phase cyclin-dependent kinase inhibitors p21 and p27 was significantly increased in the DEX-treated cells. Interestingly, two other atypical cell cycle regulators, Cdk5 and its activator p35, were increased by DEX exposure. These results suggest a mechanism for the regulation of hDG progenitor cells proliferation upon glucocorticoids increase. Studies are now being conducted to further elucidate the role of these and other cell cycle molecules in the regulation of proliferative phenomena implicated in the pathophysiology of depression and AD treatment.

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Poster

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: Otsuka Pharmaceutical Ltd

Title: Adjunctive treatment of brexpiprazole with fluoxetine can improve depression-like behaviors and dendritic changes after inflammation

Authors: M. MA[1], Q. REN[1], N. YOSHIMI[2], Y. OHGI[2], T. FUTAMURA[2], *K. HASHIMOTO[1]; [1]Chiba Univ. Ctr. Forensic Men Hlth., Chiba, Japan; [2]Otsuka Pharmaceut. Ltd, Tokushima, Japan

Abstract: Substantial clinical data support the addition of low doses of atypical antipsychotic drugs to selective serotonin reuptake inhibitors (SSRIs) to rapidly enhance the antidepressant effects in treatment-resistant patients with major depressive disorder (MDD). Brexpiprazole, a novel serotonin-dopamine activity modulator, was developed to offer efficacious and tolerable therapy for schizophrenia and adjunctive treatment of MDD. The purpose of the present study is to examine whether brexpiprazole could enhance antidepressant-like effects of the SSRI fluoxetine in depression-like behaviors and spine density in mice after the administration of lipopolysaccharide (LPS). Twenty two hours after the administration of LPS (0.5 mg/kg) or saline, vehicle, fluoxetine (10 mg/kg), brexpiprazole (0.1 mg/kg), or fluoxetine (10 mg/kg) plus brexpiprazole (0.1 mg/kg) were administered orally. Behavioral tests, including locomotion, tail suspension test (TST) and forced swimming test (FST), were performed 2-hr, 4-hr, 6-hr after drug administration, respectively. Administration of these drugs did not alter the locomotor activity in mice treated with LPS. In the TST and FST, fluoxetine or brexpiprazole alone did not alter the increased immobility time in mice treated with LPS. In contrast, combination of fluoxetine with brexpiprazole significantly decreased the increased immobility time in mice treated with LPS. Furthermore, LPS caused a reduction of spine density in prefrontal cortex (PFC), CA3 and dentate gyrus (DG) of the hippocampus, whereas LPS increased spine density in the nucleus accumbens (NAc). Although fluoxetine or brexpiprazole alone did not affect alterations in spine density in PFC, CA3, DG, and NAc after LPS administration, combination of fluoxetine with brexpiprazole significantly reversed LPS-induced alterations in the spine density in PFC, CA3, and DG. These results suggest that the combination of fluoxetine and brexpiprazole shows antidepressant-like effect in an inflammation model of depression, and that the effect may be related to enhance synaptogenesis in the PFC, CA3, and DG of hippocampus, but not NAc.

Disclosures: **M. Ma:** None. **Q. Ren:** None. **N. Yoshimi:** A. Employment/Salary (full or part-time):; Otsuka Pharmaceutical Ltd. **Y. Ohgi:** A. Employment/Salary (full or part-time):; Otsuka

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Poster

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: NIMH Grant MH087583

Title: Rapid sex- and hormone-dependent changes in signaling pathway activation and protein levels in the hippocampus following low-dose ketamine administration: a phosphoproteomics approach

Authors: *S. K. SALAND[1], R. K. SINGH[2], R. MERCER[2], T. T. LAM[3], K. WILCZAK[3], M. KABBAJ[1];
[1]Dept. of Biomed. Sci. & Program in Neurosci., [2]Translational Sci. Lab., Florida State Univ., Tallahassee, FL; [3]Dept. of Mol. Biophysics and Biochemistry, W.M. Keck Fndn. Biotech. Resource Lab., Col. of Medicine, Yale Univ., New Haven, CT

Abstract: Considerable sex bias in the risk for depression is well-established. Extending beyond prevalence and presentation, sex differences in antidepressant efficacy have also been identified that point to a role for gonadal hormones in moderating treatment response. Despite its clear importance, the precise nature of hormonal influence on antidepressant efficacy is unclear and understudied. We recently reported that female rats are more sensitive to the fast-acting antidepressant ketamine when compared to male rats, and that gonadal estrogen (E2) and progesterone (P4) are required for this heightened response. However, the mechanisms underlying this sex-dependent sensitivity to ketamine's antidepressant-like effects remain elusive. Therefore, a phosphoproteomics approach was used to identify ketamine-induced changes in signaling pathway activation and protein abundance within the dorsal hippocampus (dHPC) of intact adult male rats and female rats in either diestrus (low E2 and P4) or proestrus (high E2 and P4) stages of their estrous cycle. Tissue was collected 30 minutes following saline or an acute low dose (2.5 mg/kg) of ketamine that is behaviorally ineffective in male rats, after which total and TiO2-enriched phosphopeptide lysates were prepared and processed via high-resolution liquid chromatography-tandem mass spectrometry (LC-MS/MS) using the LTQ Orbitrap Velos. Collected LC-MS/MS data were processed and quantified (by label-free approach), and proteins identified with Progenesis QI software and MASCOT Search Engine,

respectively. Pathway and gene ontology analyses were utilized to determine how changes in protein abundances and patterns of protein phosphorylation could selectively be altered by low-dose ketamine in female as compared to male rats. Results revealed striking dissimilarities in the dHPC proteome and phosphoproteome of male and female rats both at baseline, and following low-dose ketamine treatment. Notably, these differences were heavily influenced by hormonal status in female rats. Together, these data suggest that both biological sex and the hormonal milieu are critical modulators of ketamine's rapid actions within this brain region, and provide greater insight into potential translational and post-translational processes underlying sex- and hormone-dependent modulation of ketamine's therapeutic effects. Immunohistochemical and functional studies are underway to identify region-specific changes in and functional relevance of identified proteins and pathways of interest.

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Poster

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: CIHR to LAMG (MOP102568)

Title: Ovarian hormones impart resilience against chronic stress and modulate the effects of fluoxetine on hippocampal plasticity

Authors: *R. MAHMOUD[1,2], S. R. WAINWRIGHT[1,2], J. A. CHAITON[1], S. E. LIEBLICH[1], L. A. M. GALEA[1,3,4];
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Abstract: Depression is more prevalent in women than in men, and sex differences are reported in the ability of antidepressants to alleviate symptom of depression. These findings indicate a role for gonadal hormones in the disease pathoetiology and the mechanisms underlying antidepressant efficacy. The present study investigated the effects of long-term ovarian hormone deprivation on the development of depressive-like endophenotypes and on antidepressant efficacy in female Spague-Dawley rats. Six months following ovariectomy (OVX) or sham surgery, all rats were subjected to 6 weeks of chronic unpredictable stress (CUS); a paradigm

intended to induce depressive-like phenotypes in rodents. During the last 3 weeks of CUS, rats received daily injections of fluoxetine (FLX, 5 mg/kg) or vehicle. All rats were assessed on standard measures of anxiety-, depressive-, and anhedonia-like behaviours. Our findings demonstrate that long-term ovarian hormone deprivation increased passive behaviour in the forced swim test, increased latency to feed in the novelty suppressed feeding test, and decreased sucrose preference. Further, long-term OVX resulted in a reduced dexamethasone suppression of corticosterone release, suggesting that ovarian hormones protect against chronic stress-induced impairments in the glucocorticoid-dependent negative feedback system. Finally, although fluoxetine treatment lacked behavioural and neuroendocrine efficacy, it reduced hippocampal expression of the microglial marker Iba-1, and increased several markers of hippocampal plasticity (Ki67, BrdU, and PSA-NCAM) in a region-specific and ovarian status-dependent manner. Taken together, our findings demonstrate that ovarian hormones may impart resilience against the behavioural and neuroendocrine consequences of chronic unpredictable stress, and may modulate the effects of fluoxetine on hippocampal plasticity.

Disclosures: R. Mahmoud: None. **S.R. Wainwright:** None. **J.A. Chaiton:** None. **S.E. Lieblich:** None. **L.A.M. Galea:** None.

Poster

776. Mood Disorders: Antidepressant III

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 776.19/H23

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: Israel Science Foundation (ISF 738/11

The Open University of Israel research fund

National Institute for Psycobiology in Israel (NIPI NO.7-2011-12)

Title: New Herbal Treatment for depression and Anxiety Disorders with minimal side-effects increase BDNF level in the hippocampus

Authors: *R. DORON[1], M. FRANKO[2], R. TOLEDANO[2], S. ARMOZA[3], M. REHAVI[3]; [1]The Academic Col. Tel Aviv Jaffa/The Open Unive, Tel Aviv- Jaffa, Israel; [2]Sch. of Behavioral Sci., The Academic Col. of Tel Aviv-Yaffo, Tel Aviv-Yaffo, Israel; [3]Physiol. and Pharmacology, Sackler Fac. of Med., Tel-Aviv Univ., Tel Aviv, Israel

Abstract: Anxiety and Depression disorders are prevalent and severe diseases with deleterious impact on both patients and society. Selective serotonin reuptake inhibitors (SSRIs) were shown to be effective in treating a wide spectrum of anxiety and depression disorders. Despite their therapeutic actions, SSRIs are associated with a wide variety of side effects such as weight changes, insomnia, gastrointestinal disturbances and sexual dysfunction. Furthermore, recent studies show that their success rates are not high, reaching 50% at most. Therefore, there is a clear need to explore alternative treatments for anxiety and depression disorders. We have recently produced a novel herbal mixture for the treatment of anxiety disorder. The novel treatment displayed anxiolytic and antidepressant-like effects in treated mice previously exposed to stress. The aim of the present study was to examine whether the novel treatment induce two common side effects normally induced by the conventional treatment with the SSRI escitalopram, namely, sexual dysfunction and weight gain. Mice were treated with either: (a) herbal treatment; (b) one of the four herbal components; (c) escitalopram; or (d) control group. Following treatment, sexual behavior and weight gain were evaluated in the different groups, as well as changes in prefrontal cortex serotonin transporter levels. We have found that the novel treatment has not altered sexual behavior and did not cause a weight gain, while escitalopram did lead to these two side effects. Interestingly, serotonin transporter levels in the prefrontal cortex of the escitalopram treated group were significantly lower compared to the other treatment groups. The BDNF level in the hippocampus increase after ecitalopram and herbal treatment. These results suggest that the novel treatment may have the same behavioral anxiolytic and antidepressant efficacy as SSRIs, while causing fewer side effects, possibly due to different biological mechanisms. Further studies are now conducted in order to explore the underlying biological mechanisms through which the novel treatment lead to the behavioral anxiolytic and antidepressant effects.

Disclosures: **R. Doron:** None. **M. Franko:** None. **R. Toledano:** None. **S. Armoza:** None. **M. Rehavi:** None.

Poster

776. Mood Disorders: Antidepressant III

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: Grants-in-Aid for Scientific Research Grant (C)26460328

Grants-in-Aid for Scientific Research Grant (C)24593068

Title: Long-term treatment with fluoxetine suppresses the stress response of serotonin by up-regulating dopamine D1 receptor signaling in the hippocampal dentate gyrus

Authors: Y. KAWAHARA[1], T. SHUTO[1], Y. HANADA[1], *H. KAWAHARA[2], A. NISHI[1]; [1]Pharmacol., Kurume Univ. Sch. of Medicin, Kurume, Japan; [2]Tsurumi Univ. / Sch. of Dent., Yokohama / Kanagawa, Japan

Abstract: Hippocampal serotonin (5-HT) is responsive to variety of stress and its extracellular levels are regulated by selective serotonin reuptake inhibitors (SSRIs). Long-term treatment of fluoxetine, an SSRI, has been shown to up-regulate the expression of D1 receptors in the hippocampal dentate gyrus (DG). Therefore, we investigated whether the 5-HT response to acute stress in the DG could be modulated by long-term fluoxetine treatment via mechanisms involving D1 receptors. Fluoxetine was administered for 14 days (15 mg/kg/day) and the extracellular levels of 5-HT were measured by *in vivo* microdialysis in the DG of mice using HPLC-ECD. Novelty (30 min) was applied as a stressful stimulus. In the placebo-treated group, novelty stress induced a significant increase of 5-HT to approximately 200% of basal levels. In the fluoxetine-treated group, novelty stress failed to increase 5-HT levels, but the 5-HT response to novelty stress was observed when a D1 receptor antagonist, SCH23390 (0.5 miroM), was continuously infused into the DG. Local infusion of a D1 receptor agonist SKF81297 (10 microM) which did not affect the 5-HT levels in the placebo-treated group, induced a significant decreased of the 5-HT levels in the fluoxetine-treated group. The results demonstrate that long-term treatment of fluoxetine suppresses the 5-HT response to novelty stress by up-regulating D1 receptor signaling in the DG. Such interaction of 5-HT and dopamine system may be involved in therapeutic effects of SSRIs.

Disclosures: Y. Kawahara: None. **T. Shuto:** None. **Y. Hanada:** None. **H. Kawahara:** None. **A. Nishi:** None.

Poster

776. Mood Disorders: Antidepressant III

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Program#/Poster#: 776.21/H25

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: MH099085

Title: Ovarian hormones influence sensitivity to the antidepressant-like effect of low dose ketamine in C57BL/6 mice

Authors: *A. M. DOSSAT, K. N. WRIGHT, C. E. STRONG, M. KABBAJ;
Biomed. Sci., Florida State Univ., Tallahassee, FL

Abstract: Ketamine, an NMDA receptor antagonist, has shown great promise as a rapid-acting antidepressant compound. Despite the wealth of knowledge recently acquired regarding the antidepressant efficacy of ketamine, it is still not clear if there are gender differences in sensitivity to ketamine's antidepressant effects. This is a critical gap in our knowledge regarding the clinical application of this compound because it has long been established that females are twice as likely to suffer from depression as compared to males. Our group previously showed that female rats are more sensitive to the antidepressant-like effects of ketamine, an effect that was mediated by ovarian hormones. The purpose of the current study was to examine potential sex differences in sensitivity to low dose ketamine in mice, as well as clarify the contribution of ovarian hormones to this sensitivity. We used a mouse model to take advantage of the natural peaks of progesterone (P4) and estrogen (E2) that occur on distinct days. Female mice were lavaged daily for at least two cycles to determine what phase of the estrous cycle they were in. In experiment 1 females in either diestrus 1 (D1), diestrus 2 (D2), proestrus (P), estrus (E) and males were treated with 0, 1.5, or 3 mg/kg ketamine 30 min prior to a forced swim test (FST). Males and females in D1 exhibited an antidepressant-like profile to 3 mg/kg ketamine. However, females in D2 (peak of P4) displayed an antidepressant-like response to both 1.5 and 3 mg/kg ketamine. Females in P (peak of E2) displayed an antidepressant-like profile in the vehicle condition, with no additional effect of any dose of ketamine. In experiment 2 females were treated with an estrogen receptor (ER) α (PPT) or ERβ (DPN) agonist when in D1, to take advantage of the natural nadir of gonadal hormones during this estrous phase; 24 h later these animals received a subthreshold dose of ketamine (1.5 mg/kg) 30 min prior to the FST. Females in D1 did not display an antidepressant-like profile after 1.5 mg/kg ketamine, PPT, or DPN administration. However, following treatment with both PPT and DPN, females displayed a significant response to the sub-threshold dose of ketamine. These results suggest that both ERα and ERβ play a role in enhancing sensitivity to ketamine and future experiments are aimed at differentiating the functional roles of these receptor subtypes. Current research is aimed at elucidating the neural mechanism(s) underlying the enhanced sensitivity to ketamine observed in females that are simultaneously experiencing an endogenous flux of ovarian hormones, with a focus on brain-derived neurotrophic factor in the prefrontal cortex and hippocampus.

Disclosures: **A.M. Dossat:** None. **K.N. Wright:** None. **C.E. Strong:** None. **M. Kabbaj:** None.

Poster

776. Mood Disorders: Antidepressant III

Location: Hall A

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Program#/Poster#: 776.22/H26

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Modulation of hypothalamic neurogenesis by stress and antidepressants: the relevance in energy balance regulation in depression

Authors: M. MORAIS, A. MATEUS-PINHEIRO, P. PATRÍCIO, L. PINTO, N. SOUSA, *J. BESSA;
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Abstract: Major depression is associated with critical changes in appetite and body weight, which are differentially regulated by distinct classes of antidepressants (AD). The hypothalamus is the key brain region involved in energy balance regulation and has been described as a novel neurogenic region (1). However, the possible modulation of hypothalamic neurogenesis by stress and antidepressant treatment is yet to be explored. In the present study, we aimed to address this by exploring hypothalamic neurogenesis in animals submitted to chronic mild stress (CMS) and treated with the antidepressants fluoxetine and imipramine (2). These analyses were performed in the arcuate (ARC) and median eminence (ME) nuclei of the hypothalamus, neurogenic regions that have recently been implicated in energy balance regulation (3). Additionally, the relevance of the functional phenotype of these newborn neurons was assessed by the co-expression with NPY, POMC and leptin receptors. The results revealed that stress and antidepressant treatment induced significant changes in food intake and body weight gain. Animals exposed to stress presented no differences in the total food intake but revealed significant body weight loss. Treatment with AD differentially regulated these phenomena. While fluoxetine reduced total food intake and body weight gain, imipramine restored total food intake and increased body weight gain. In addition, the circadian disruption of feeding patterns in stressed animals was reversed by both AD. Regarding the impact in the brain, the results revealed that stress and AD differentially modulate hypothalamic neurogenesis in the ARC and ME nuclei. Stressed animals displayed an increase in newborn neurons in the ARC and a decrease in the ME. Interestingly, only imipramine was able to revert these neuroplastic effects. In summary, this work demonstrates that CMS and AD treatment can modulate hypothalamic neurogenesis in two different hypothalamic nuclei involved in energy homeostasis.. Furthermore, a differential effect in hypothalamic neurogenesis was observed with different classes of antidepressants. 1.Kokoeva MV, Yin H, Flier JS. Neurogenesis in the hypothalamus of adult mice: potential role in energy balance. Science (New York, NY) 2005; 310(5748): 679-683. 2.Bessa JM, Ferreira D, Melo I et al. The mood-improving actions of antidepressants do not depend on neurogenesis but are associated with neuronal remodeling. Mol Psychiatry 2009; 14(8): 764-773, 739. 3.Lee DA, Bedont JL, Pak T, Wang H, et al. Tanycytes of the hypothalamic median eminence form a diet-responsive neurogenic niche. Nature neuroscience 2012; 15(5): 700-702.

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Poster

776. Mood Disorders: Antidepressant III

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Program#/Poster#: 776.23/H27

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Antidepressants activate matrix metalloproteinase (MMP) in astroglial cells: involvement in glial cell line-derived neurotrophic factor (GDNF) expression

Authors: H. ABE[1,2], *K. HISAOKA[1], N. KAJITANI[2], M. OKADA-TSUCHIOKA[2], K. ITAGAKI[2,3], M. MORIOKA[1], Y. NAKATA[1], M. TAKEBAYASHI[2,3];
[1]Dept. Pharmacol. Hiroshima Univ., Hiroshima, Japan; [2]Div. of Psychiatry and Neuroscience, Inst. for Clin. Res., NHO Kure Med. Ctr., Kure, Japan; [3]Dept. of Psychiatry, NHO Kure Med. Ctr., Kure, Japan

Abstract: [Background] Matrix metalloproteinases (MMPs), a family of enzymes that regulate the extracellular matrix (ECM), are involved in higher-order brain function through a shedding of extracellular matrix proteins, such as growth factors. Recently, both clinical and animal studies demonstrated glial plasticity to be important for the therapeutic action of antidepressants. We previously reported that antidepressants increase glial cell line-derived neurotrophic factor (GDNF) production possibly through a shedding of the fibroblast growth factor receptor (FGFR) ligands by MMPs (Hisaoka et al., 2011). The current study clarifies the types of MMPs and cellular mechanisms that lead to GDNF production following antidepressant treatment in astroglial cells. [Methods] Rat C6 cells and primary astrocytes were used in the following experiments. We measured the level of GDNF mRNA by real-time PCR and the activity of MMP-2 and MMP-9 by gelatin-zymography. [Results] Amitriptyline (a tricyclic antidepressant)-induced GDNF mRNA expression was significantly inhibited by broad-spectrum MMP inhibitors (GM6001 and prinomastat). RT-PCR revealed that both rat C6 cells and primary astrocytes express the GM6001-sensitive MMPs, including MMP-2, 3, 9. In C6 cells, amitriptyline-induced GDNF mRNA expression was significantly and completely inhibited by a MMP-9 inhibitor or MMP-3 inhibitors, whereas a MMP-2 inhibitor had no effect. Treatment with amitriptyline increased acute and time-dependent MMP-9 activity around twofold level, but not MMP-2 activity. Amitriptyline-induced MMP-9 activation was completely blocked by MMP-3 inhibitors. Furthermore, treatment with exogenous MMP-3 or MMP-9 significantly

increased GDNF mRNA expression, but exogenous MMP-2 had no effect. In rat primary astrocytes, treatment with amitriptyline or several different classes of antidepressants also increased MMP-9 activity. [Conclusion] These results demonstrated that the MMP-3/MMP-9 cascade is crucial in amitriptyline-induced GDNF mRNA expression. Our data suggest the possible existence of a novel MMP-related target in astrocytes for antidepressants, leading to activation of GDNF production.

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Poster

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: NSFC Grant 81301164

NIH Grant MH100583

Title: Adiponectin is required for PPARγ-mediated effects on depression- and anxiety-related behaviors

Authors: *M. GUO[1], D. ZHAO[1], R. DING[1], M. WANG[1], X.-Y. LU[2,1];
[1]Binzhou Med. Univ. Hosp., Shandong, China; [2]Pharmacol., Univ. of Texas Hlth. Sci. Ctr. at San Antonio, San Antonio, TX

Abstract: Our previous studies have shown that the levels of adiponectin, an adipocyte-derived hormone, are low in animal models of depression and adiponectin deficiency increases susceptibility to depressive-like behaviors. Rosiglitazone is a peroxisome proliferator-activated receptor gamma (PPARγ) agonist widely used for the treatment of type 2 diabetes. Rosiglitazone stimulates de novo production of adiponectin. In this study, we examined the effects of rosiglitazone on depressive- and anxiety-like behaviors and whether such effects require adiponectin. In the forced swim (FST) test, rosiglitazone was administered intraperitoneally (i.p.) 3 times within 24 h following the pretest. Rosiglitazone treatment significantly reduced immobility time in the FST, accompanied by increased plasma adiponectin levels. The antidepressant-like effect of rosiglitazone in the FST was abolished in adiponectin knockout mice. Moreover, rosiglitazone treatment in wild-type mice decreased the latency to approach and

eat a familiar food in the novelty-suppressed feeding test and increased time and entries to open arms in the elevated-plus maze test. These anxiolytic effects of rosiglitazone were also abolished in adiponectin knockout mice. Taken together, these results demonstrate that adipocyte-derived adiponectin is required for PPARγ-mediated effects on depressive- and anxiety-like behaviors.

Disclosures: **M. Guo:** None. **D. Zhao:** None. **R. Ding:** None. **M. Wang:** None. **X. Lu:** None.

Poster

776. Mood Disorders: Antidepressant III

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 776.25/H29

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Vortioxetine increases synaptic glutamate neurotransmission without altering extrasynaptic glutamate concentrations

Authors: *A. L. PEHRSON, E. DALE, S. LEISER, C. SANCHEZ;
Lundbeck Res. USA, Paramus, NJ

Abstract: Vortioxetine is a multimodal-acting antidepressant that has shown beneficial effects on cognitive functions in clinical studies. Although it acts through purely serotonergic receptor mechanisms at clinically relevant doses (5-HT1D, 5-HT3, and 5-HT7 receptor antagonism, serotonin (5-HT) transporter inhibition, 5-HT1B receptor partial agonism and 5-HT1A receptor agonism), recent work suggests that these serotonergic actions indirectly modulate glutamate neurotransmission in a cognition-relevant way. This poster presents an overview of data suggesting that vortioxetine selectively increases synaptic glutamate neurotransmission without altering extrasynaptic glutamate, and reverses cognitive deficits induced by glutamate dysregulation. Vortioxetine and the SSRI escitalopram were compared in terms of long-term potentiation (LTP), 5-HT-mediated inhibitory postsynaptic currents (IPSCs) in hippocampal pyramidal neurons, cortical pyramidal neuron firing rates, and gamma band oscillatory power. Given vortioxetine's effects in these glutamate neurotransmission-sensitive models, cortical and hippocampal extracellular glutamate concentrations were investigated via microdialysis. Finally, vortioxetine's ability to reverse glutamate-related cognitive dysfunction was investigated using models including MK-801-induced social recognition memory deficits and subchronic PCP-induced attentional set shifting impairments.Vortioxetine significantly enhanced LTP and reduced the frequency and amplitude of 5-HT-mediated IPSCs in hippocampal pyramidal cells. Acute vortioxetine treatment also increased the firing rate of cortical pyramidal neurons [1] and enhanced gamma oscillatory power *in vivo*. The SSRI escitalopram had no effects on LTP, 5-HT

mediated IPSCs, cortical pyramidal neuron firing [1] or gamma oscillations. Despite the vortioxetine induced changes in these glutamate neurotransmission-sensitive models, no effect was found on cortical or hippocampal extracellular glutamate concentrations. Finally, vortioxetine reversed MK-801-induced memory deficits and subchronic PCP-induced impairments in attentional set shifting.These data suggest that vortioxetine, unlike the SSRI escitalopram, enhances synaptic glutamate neurotransmission in a manner that is relevant for cognitive function. However, vortioxetine's lack of effect on extracellular glutamate concentrations suggests that it selectively modulates synaptic vs. extrasynaptic glutamate neurotransmission.References: [1] Riga M, Celada P, Sanchez C, Artigas F European Neuropsychopharmacol 23:S393-4

Disclosures: **A.L. Pehrson:** A. Employment/Salary (full or part-time):; Lundbeck Research USA, Inc. **E. Dale:** A. Employment/Salary (full or part-time):; Lundbeck Research USA, Inc. **S. Leiser:** A. Employment/Salary (full or part-time):; Lundbeck Research USA, Inc. **C. Sanchez:** A. Employment/Salary (full or part-time):; Lundbeck Research USA, Inc.

Poster

776. Mood Disorders: Antidepressant III

Location: Hall A

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: JSPS KAKENHI 26860951

JSPS KAKENHI 24791244

Title: Dopamine D1 receptor activation enhances antidepressant effects of SSRI in a mouse model of depression

Authors: *T. SHUTO, M. KUROIWA, N. SOTOGAKU, A. NISHI;
Kurume Univ., Kurume, Japan

Abstract: Selective serotonin reuptake inhibitors (SSRIs) act as antidepressants by modulating monoamine system. However, the ability of SSRIs to improve symptoms of depression is limited. Chronic administration of SSRI is recently found to increase dopamine D1 receptor expression and upregulate D1R signaling in the hippocampal dentate gyrus, one of the main target brain regions of antidepressants, in C57BL/6 mice. Therefore, we performed behavioral studies to investigate the role of dopamine D1 receptors in anti-depressant action of an SSRI,

fluoxetine. Depression-like behaviors were evaluated with novelty-suppressed feeding test and tail suspension test in a chronic restraint stress mouse model of depression. Chronic treatment with fluoxetine (15 mg/kg/day, 14 days) alone showed anti-depressant effect in mice subjected to mild restraint stress (2 hr/day, 14 days), but not to strong restraint stress (4 hr/day, 28 days). However, chronic co-administration of a dopamine D1 receptor agonist, R(+)-SKF81297 (1.5 mg/kg/day), with fluoxetine showed anti-depressant effects in mice subjected to strong restraint stress. In addition, acute injection of SKF81297 at 3.0 mg/kg induced behavioral seizures only in chronically fluoxetine-treated mice, suggesting that chronic fluoxetine treatment lowered the seizure threshold for D1 receptor activation. These results suggest that activation of dopamine D1 receptor signaling in the dentate gyrus ameliorates depression-like behaviors by enhancing antidepressant effects of SSRI under SSRI-resistant stress conditions.

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Poster

776. Mood Disorders: Antidepressant III

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: Grant-in-Aid for Exploratory Research (24659548)

Title: An inverted cAMP-response element (CRE)-mediated transcriptional regulation of the human tryptophan hydroxylase-2(TPH2) gene

Authors: H. KANEKO[1], M. ODA[2], Y. NAWA[3], T. HIROI[3], T. KUMAI[2], R. TAKAHASHI[4], *H. MATSUI[5];
[1]Inst. RI Res., St. Marianna Univ. Grad Med., Kawasaki, Japan; [2]Dep PGx, [3]Inst. RI Res., St. Marianna Univ. Grad Sch. Med., Kawasaki, Japan; [4]Dep Biochem, Fac Pharm Sci, Toho Univ., Funahashi, Japan; [5]Dept Mol Behav Neurosci, St. Marianna Univ. Grad Sch. Med., Kawasaki, Kanagawa, Japan

Abstract: The central serotonin (5-hydroxytryptamine, 5-HT) system modulates diverse physiological functions, including of regulation of sleep, rhythm, appetite, learning, memory and emotion. Dysfunction of the 5-HT system in the brain has been implicated in the etiology of the wide range of neurodevelopmental disorders, including depression, anxiety, obsessive-compulsive disorder, autism, and schizophrenia. As the rate-limiting enzyme for the synthesis of central 5-HT, TPH2 plays a pivotal role in the modulation of 5-HT neurotransmission and is thus

a promising target for the therapeutic treatment of neuropsychiatric disorders. Previously we demonstrated that the expression of the human TPH2(hTPH2) gene is strictly controlled through the NRSF-mediated negative regulation in immortalized rat serotonergic RN46A cells (a generous gift from Dr. Whittemore SR., Univ Louisville, KY). However, the mechanism by which hTPH2 gene expression is activated remains unresolved. Sequence analysis revealed an inverted CRE (5'-TAACGTCA-3') in the hTPH2 promoter (-243/-236 relative to the transcription start site). Interestingly, potential CREs were also found at corresponding positions of the mouse (-374/-367, 5'-TAACGTCA-3') and rat (-203/-196, 5'-TGACGCAT-3') TPH2 genes. This prompted us to examine how the hTPH2 gene promoter activity changes by CRE-mediated signaling pathways in RN46A cells. A 2-kb promoter region of the hTPH2 gene (-1850/+141) was cloned into pGL4-Basic (TPH2-55) and a mutant having deletion of its 5'-untranslated region (+10/+121; a region containing potential repression elements) was constructed (TPH2-100). A series of mutant constructs with nucleotide substitutions in the CRE was made. Promoter activities were assessed by transient transfections into RN46A cells. Whereas overexpression of CREB (CRE binding protein) alone showed marginal effects, overexpression of PKA-alpha (cAMP-dependent protein kinase catalytic subunit alpha) alone increased TPH2-100 promoter activity. Simultaneous overexpression of CRTC (CREB regulated transcription coactivator) in addition to PKA-alpha and CREB further enhanced TPH2-100 promoter activity. Gel mobility shift assays confirmed the CREB binding to the relevant element. These results indicate that the CRTC plays a critical role in positively regulating the hTPH2 promoter activity through associating with CREB on the inverted CRE of the hTPH2 promoter region and the subsequent 5-HT synthesis in the brain.

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Poster

776. Mood Disorders: Antidepressant III

Location: Hall A

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Program#/Poster#: 776.28/H32

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: The grant from Grants-in-Aid for Scientific Research on Innovative Areas of The Ministry of Education, Culture, Sports, Science and Technology, Japan (to K.H., Grant number: 24116006)

Title: R-ketamine: a novel rapid and long-lasting antidepressant

Authors: C. YANG[1], *Y. SHIRAYAMA[2], J.-C. ZHANG[1], Q. REN[1], M. MA[1], W. YAO[1], C. DONG[1], K. HASHIMOTO[1];
[1]Chiba Univ. Ctr. Forensic Men Hlth., Chiba, Japan; [2]Teikyo Univ. Chiba Med. Ctr., Chiba, Japan

Abstract: The NMDA receptor antagonist ketamine shows rapid and robust antidepressant effects in treatment-resistant patients with major depression and bipolar disorder, indicating that ketamine is the most attractive antidepressant. Ketamine (or RS (±)-ketamine) is a racemic mixture containing equal parts of R (-)-ketamine and S (+)-ketamine. S-ketamine has an approximately 4-fold greater affinity for the NMDA receptor than the R-isomer. Furthermore, S-ketamine shows an approximately 3-4 fold greater anesthetic potency and greater undesirable psychotomimetic side effects, compared with the R-isomer. Recently, we reported that, compared with S-ketamine, R-ketamine produced rapid and long-lasting antidepressant effects in juvenile mice exposed neonatally to dexamethasone (Zhang et al., 2014). In this study, we examined the effects of R- and S-ketamine in the social defeat stress and learned helplessness (LH) models of depression. Behavioral tests, including the tail suspension test (TST), forced swimming test (FST), and 1% sucrose preference test, were performed. Although both isomers of ketamine showed antidepressant-like effects in the social defeat stress model, R-ketamine was more potent than S-ketamine. Seven day after a single does, R-ketamine was more potent than S-ketamine. Furthermore, R-ketamine, but not showed antidepressant-like effect in the rat LH model. In the behavioral tests for side effects, S-ketamine, but not R-ketamine, caused hyperlocomotion, prepulse inhibition deficits, and rewarding effect. In conclusion, a single dose of R-ketamine produced rapid and long-lasting antidepressant effects in the social defeat stress and LH models of depression. Therefore, R-ketamine appears to be a potent and safe antidepressant relative to S-ketamine, since R-ketamine is free of psychotomimetic side effects.

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Poster

777. Alcohol and Cannabis: Effects of Exposure During Adolescence

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 777.01/H33

Topic: C.17. Drugs of Abuse and Addiction

Support: Start-up funds-Kansas State University

Title: Alcohol access in adolescence and early adulthood does not affect sign-tracking, but augments omission contingency learning, in rats

Authors: *P. E. KALLENBERGER, N. BRIGHT, H. FISHER, M. GREER, A. LIMOGES, A. PAJSER, C. L. PICKENS;
Kansas State Univ., Manhattan, KS

Abstract: Problem: Alcohol use in humans is associated with impaired response inhibition in self-reports of every-day life and in laboratory tasks. In humans, it is difficult to determine whether alcohol consumption leads to response inhibition impairments or if the response inhibition impairments lead to increased alcohol consumption. We tested rats with previous adolescent/early adult alcohol access in a procedure where there was no requirement to press a lever associated with the delivery of food (sign-tracking task), and then assessed the rats' abilities to inhibit these responses (omission contingency task). We assessed whether alcohol consumption correlates with sign-tracking or if alcohol access might alter responses in these tasks. Methods: Rats were given access to alcohol using a chronic intermittent access procedure (24-hr access to 20% alcohol 3X per week, separated by 24-48 hr periods where no alcohol is available) or water alone for six weeks (PND 26-66). Three days after the final alcohol period, rats began food restriction, and then began sign-tracking training 10 days later. The rats received six days of sign-tracking training. Next, the rats received six days of omission contingency training. During the omission contingency sessions, one lever was paired with food only if the rat did not press the lever while it was available. Results: We did not find any significant correlations between the amount of alcohol consumed and behavior in either the sign-tracking or omission contingency task. We also did not observe any effect of prior alcohol access on sign-tracking behavior. However, we did observe a significant effect of prior alcohol access (vs. water access alone) on the rate of omission training, such that rats with prior alcohol access learned more quickly to inhibit their responding to the lever on the omission contingency. Conclusion: Our results suggest that alcohol consumption in adolescence and early adulthood can lead to faster omission contingency learning. This replicates a previous effect seen in mice given chronic intermittent exposure to alcohol via vapor chambers (DePoy et al., 2013), but it is unclear whether this effect reflects alterations in response inhibition abilities or some change in the representations that guide sign-tracking behavior. Future research will determine whether alterations in omission contingency performance occur after alcohol consumption in adulthood and also investigate the neurobiological basis of alcohol's effects.

Disclosures: **P.E. Kallenberger:** None. **N. Bright:** None. **H. Fisher:** None. **M. Greer:** None. **A. Limoges:** None. **A. Pajser:** None. **C.L. Pickens:** None.

Poster

777. Alcohol and Cannabis: Effects of Exposure During Adolescence

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 777.02/H34

Topic: C.17. Drugs of Abuse and Addiction

Support: NIH AA017359

Title: Acute ethanol exposure in adolescent female rats alters fear conditioning in an age dependent manner

Authors: J. A. TRAVIS[1], K. ISHIWARI[2], *R. SIRCAR[1,2];
[1]The City Col. of New York, New York, NY; [2]Albert Einstein Col. of Med., Bronx, NY

Abstract: Earlier, our lab and others have reported that ethanol treatment in adolescent female rat causes hippocampus-associated spatial memory deficit when tested in the hidden platform task of the Morris water maze. Adult rats did not show any such deficit. Ethanol in adolescent rats also impairs memory functions during fear conditioning. Adolescent female rats treated acutely with ethanol and subjected 30 minutes later to a couple of tone-shock pairings in the fear conditioning paradigm, showed significant disruptions specifically in the hippocampus-related contextual memory but not in the amygdala-associated cued fear paradigm. The present study was undertaken to determine the effects of ethanol on fear conditioning in younger and older adolescent rats. Thirty minutes prior to training in the fear conditioning paradigm, both young and older adolescent rats were treated with a single intraperitoneal injection of ethanol (2g/kg). Control rats received equivalent volumes of vehicle. Twenty four hours later, all rats were tested for (i) contextual fear in the same training chamber, and (ii) cued fear in a novel chamber along with exposure to tone. For each rat, freezing during contextual and cued fear conditionings were recorded. Freezing was used as a measure of memory; more freezing indicates better memory. Younger adolescent female rats treated with ethanol showed significant impairments in contextual fear. There was little effect on cued memory. On the other hand, older adolescent rats exhibited impairments in both contextual as well as cued fear conditionings. Together, these data suggest a differential behavioral effect of ethanol on memory functioning in younger vs. older adolescent rats.

Disclosures: **J.A. Travis:** None. **K. Ishiwari:** None. **R. Sircar:** None.

Poster

777. Alcohol and Cannabis: Effects of Exposure During Adolescence

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 777.03/H35

Topic: C.17. Drugs of Abuse and Addiction

Support: NIH RO1 AA021517

NIH T32 AA013527

Title: The long-term effects of adolescent binge alcohol exposure on anxiety behavior in male Wistar rats

Authors: *A. R. TORCASO, A. ASIMES, E. PINCETI, Y. S. RAO, C. L. SHULTS, C. K. KIM, T. R. PAK;
Cell and Mol. Physiol., Loyola Univ. Chicago, Maywood, IL

Abstract: Binge drinking during adolescence is a common occurrence which is associated with increased risk of developing alcohol dependence and other mental health disorders. Hypothalamo-pituitary-adrenal (HPA) axis dysfunction is one characteristic commonly observed in many affective disorders, including anxiety and depression. Our laboratory has previously demonstrated that adolescent binge-pattern alcohol exposure results in long-term dysfunction of the HPA axis in a Wistar rat model. However, it was not determined in those studies if the rats would exhibit increased anxiety-like behaviors, in accordance with observations based on human adolescent binge drinkers. Therefore, the current study aimed to measure anxiety behaviors in young adult male Wistar rats that had received binge-pattern alcohol treatment as adolescents with no further perturbation, and furthermore to observe the behavioral and neuroendocrine responses to a heterotypic psychological stressor in these rats. Following a week of handling, rats were exposed to an eight day binge-pattern alcohol paradigm from post-natal day (PND) 37-44, which has been previously used in our laboratory, or received water as a control. The rats were un-manipulated for three weeks, then handled again for one week prior to behavioral testing. Around PND 72, anxiety behaviors were measured using the elevated-plus maze (EPM) equipped with a video camera and tracking software. The following day, half the rats from each group (binge-treated or water-treated) were placed in a plastic restraint tube for 30 minutes, or as a control were placed individually in a new cage, then were immediately tested again in the EPM. Compared to controls, the binge-treated rats spent less time in the open arms and more time in the intersection of the four arms. Following EPM testing, the rats were euthanized by rapid decapitation, and the brain and trunk blood were collected. Plasma corticosterone (CORT)

levels were measured by ELISA. Two-way ANOVA revealed a statistically significant effect of alcohol exposure or restraint stress on CORT levels, but there was no significant interaction between the two independent variables. Taken together, these data suggest that rats with prior adolescent binge alcohol exposure not only have long-term dysfunction of the neuroendocrine response to stress, they also exhibit increased anxiety behaviors under stress.

Disclosures: **A.R. Torcaso:** None. **A. Asimes:** None. **E. Pinceti:** None. **Y.S. Rao:** None. **C.L. Shults:** None. **C.K. Kim:** None. **T.R. Pak:** None.

Poster

777. Alcohol and Cannabis: Effects of Exposure During Adolescence

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 777.04/H36

Topic: C.17. Drugs of Abuse and Addiction

Support: AA018779

Title: Adolescence chronic caffeine exposure increases alcohol drinking and depressive-like behavior in mice

Authors: ***D. J. HINTON**, Y. CHOI, A. OLIVEROS, C. A. VADNIE, S. CHOI, D.-S. CHOI; Mayo Clin. Col. of Med., Rochester, MN

Abstract: During adolescence, dysregulation of neurotransmitter systems could alter the maturation of brain circuits involved in reward, mood and cognitive behaviors. Caffeine is the most commonly consumed drug in the world. Despite several notable beneficial effects of acute caffeine that have been documented in adults, excessive caffeine consumption during adolescence has been shown to be associated with psychiatric disorder symptoms which include attention deficit hyperactivity disorder, anxiety, aggressiveness, sleep disturbances and addiction. Adolescent mice self-administered caffeine (1 mg/ml) for 16 weeks beginning at 4 weeks of age. We found that chronic caffeine-exposed mice showed reduced motivation to explore a novel environment compared to mice consuming water (control mice). Mice chronically consuming caffeine also had less motivation to walk on the accelerating rotarod compared to control mice. Caffeine-exposed mice buried less marbles in the marble-burying test, suggesting that chronic caffeine reduced attentive behaviors. Furthermore, caffeine consuming mice showed reduced motivation to escape the forced swim test suggesting the presence of depression-like behavior compared to control mice. In addition, caffeine consuming mice exhibited anxiety-like behavior as they spent significantly less time in the center zone of a novel open-field chamber and less

time in the open arm of the elevated plus maze compared to control mice. In Pavlovian association experiments, mice chronically consuming caffeine exhibit increased impulsive behavior to obtain a hedonic reward (20% sucrose). Finally, caffeine was removed from the diet for 1 week and mice were presented with a two-bottle choice ethanol drinking experiment. The concentration of ethanol was raised every fourth day, increasing from 3 to 6 to 10 to 15 to 20% (v/v) ethanol. Mice that were previously exposed to caffeine consumed and preferred significantly more ethanol than mice that previously only drank water. Overall, these data indicate that chronic inhibition of adenosine receptors during adolescence may contribute to increased impulsivity and ethanol consumption as well as anxiety- and depressive-like behaviors in adult mice.

Disclosures: **D.J. Hinton:** None. **Y. Choi:** None. **A. Oliveros:** None. **C.A. Vadnie:** None. **S. Choi:** None. **D. Choi:** None.

Poster

777. Alcohol and Cannabis: Effects of Exposure During Adolescence

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIAAA AA019972-01 to LPS

Title: Adolescent ethanol exposure, pubertal timing, and novelty seeking in adulthood

Authors: *E. KIM, L. P. SPEAR;
Binghamton Univ., Binghamton, NY

Abstract: Adolescence-typical behaviors such as high novelty seeking are associated with increased risk for using drugs of abuse. Animal studies have shown that adolescent intermittent ethanol exposure (AIE) sometimes leads to retention of adolescent-like phenotypes into adulthood, perhaps increasing propensity for later alcohol use disorders. Research in humans has implicated pubertal timing in distinct behavioral outcomes, including drug/alcohol use. Given that ethanol (EtOH) may alter neural substrates underlying the timing of sexual maturation, the present study assessed whether AIE alters pubertal status, potentially contributing to the long term behavioral consequences of AIE. Male and female Sprague-Dawley rats were intubated with 4.0 g/kg of EtOH (25% v/v) (AIE), water (H20) or non-intubated (NI) every other day from postnatal (P)25-45. All rats were weighed and assessed daily until P50 for physical signs of sexual maturation (first day of vaginal opening [VO] in females and partial or complete balano

preputial skinfold separation [BPS] in males). Additional controls (CTRL) for behavioral testing were only handled on P25 and 45. On P70, all animals were given a novel object test and assessed for latency to contact, time spent sniffing and in contact with the object, as well as locomotor activity. While no differences were seen in mean age of partial BPS, AIE and H2O males completed BPS at significantly younger ages than NI males. Females in the H2O group exhibited VO at a younger age than NI females; this apparent intubation effect was reversed by EtOH, with no significant differences between AIE and NI females. In novel object testing in adulthood, NI males contacted the object more quickly than their female counterparts, a sex difference that did not reach significance in the other experimental groups. Although the novelty seeking behaviors were not affected by AIE, further analysis revealed that pubertal status predicted behavioral outcomes within treatment groups for males but not females. Delayed time to partial BPS was positively correlated with time spent sniffing in EtOH males, and object contact in EtOH and H2O treated males. Time to complete BPS was positively correlated with time spent sniffing and in contact in EtOH males only. These data further demonstrate the role of pubertal status in novelty seeking behaviors and provide evidence for the contribution of altered pubertal timing after exposure to EtOH in the later expression of novelty seeking behaviors.

Disclosures: E. Kim: None. **L.P. Spear:** None.

Poster

777. Alcohol and Cannabis: Effects of Exposure During Adolescence

Location: Hall A

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Title: Concurrent ethanol-nicotine intake by peri-adolescent p rats confers resistance to extinction of intravenous nicotine self-administration in adulthood

Authors: E. A. ENGLEMAN, A. M. SENTIR, M. D. WHITE, Z. A. RODD, R. A. CHAMBERS, *R. L. BELL;
Dept. of Psychiatry, Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: Abuse of ethanol (Et) and nicotine (NIC) during adolescence appear to have deleterious long-range consequences extending into adulthood. The objective of the current study was to examine the long-range consequences of peri-adolescent (P-A) Et-NIC co-abuse in alcohol-preferring (P) rats. P-A female P rats were randomly divided into 5 drinking groups (3-drinking bottles available concurrently): Water [W--W--W (W)], 10% sucrose [W--10% S--10% S (S)], 10% sucrose + 0.07 mg/ml and 0.14 mg/ml NIC [W--0.07 mg/ml NIC & 10% S--0.14 mg/ml NIC & 10% S (NS)], 15% (v/v) Et [W--15% Et--15% Et (E)], and 0.07 mg/ml and 0.14 mg/ml NIC + 15% Et [W--0.07 mg/ml NIC & 15% Et--0.14 mg/ml NIC & 15% Et (NE)]. From post-natal day (PND) 30 to 60, rats received two scheduled 1hr access periods, during the dark cycle each day, to their respective solutions (Monday-Friday) with ad lib access to water and food. Rats in the NS and NE groups averaged 8.5 ± 1 and 7.2 ± 1 mg/ml NIC intake, respectively, per day. Et intake averaged 8.2 ± 1 and 7.1 ± 1 g/kg body weight/day for the E and NE groups, respectively. All rats were then double-housed in plastic cages with free access to food and water only until ~PND 74 when all rats were implanted with intravenous (IV) catheters. On PND 80, rats began a 3 week acquisition/maintenance phase of operant IV self-administration (IVSA) of 0.015 mg NIC/kg/infusion (FR1) - daily 2 hr sessions, 5 days/week. After 3 weeks of NIC IVSA, all rats began the 2 week extinction phase of the experiment which proceeded exactly as in the acquisition phase, except no NIC was infused after any lever press. Rats from all groups acquired the NIC IVSA behavior; however, rats in the NE P-A drinking group showed significantly greater NIC IVSA as adults than any of the other P-A drinking groups. Compared with the other groups, total responding on the active lever during the extinction phase was greater for the NE group (715 ± 114/10 sessions, mean ± SEM) compared to the W (439 ± 54), S (466 ± 44), NS (502 ± 74), and E (492 ± 51) groups [ANOVA followed by planned post-hoc tests, $p < 0.05$]. The greater resistance to extinction displayed by the NE group suggests that P-A NIC-Et co-abuse produces a unique effect by enhancing the conditioned reinforcing effects of cues associated with NIC IVSA in adulthood; whereas P-A NIC or P-A Et did not exert this effect. Thus, P-A NIC-Et may enhance the salience of environmental cues conditioned to NIC-induced effects, or vice versa, driving NIC relapse behavior in those with a genetic predisposition for alcohol-abuse and -dependence.

Disclosures: **E.A. Engleman:** None. **A.M. Sentir:** None. **M.D. White:** None. **Z.A. Rodd:** None. **R.A. Chambers:** None. **R.L. Bell:** None.

Poster

777. Alcohol and Cannabis: Effects of Exposure During Adolescence

Location: Hall A

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Program#/Poster#: 777.07/H39

Topic: C.17. Drugs of Abuse and Addiction

Support: DEARC PROGRAM STATE UNIVERSITY OF NEWYORK

Title: Sex and age-dependent modulatory effects of maternal care on ethanol preference and sensitivity to ethanol-induced sedation hypnosis

Authors: *D. O. POPOOLA[1], N. M. CAMERON[2];
[1]Binghamton Univ., Endicott, NY; [2]Psychology, State Univ. of New York, Binghamton, NY

Abstract: We investigated the influence of natural variations in maternal care on ethanol consumption and sensitivity to ethanol-induced sedation. Long Evans litters were categorized into high or low licking and grooming (LG). Using a free two-bottle choice test, high and low offspring were tested for 5% v/v ethanol consumption and preference for four weeks (PND 32-57). Using the loss of righting reflex (LORR) paradigm, offspring were tested at PND 42 (mid-adolescence) for sensitivity to acute 20% v/v ethanol-induced sedation at 3.0g/kg and 3.5g/kg ethanol dose. Male offspring were also tested with LORR at 3.0g/kg or 3.5g/kg ethanol dose at PND 50 (late adolescence), and 3.0 g/kg at PND 92-95 (adulthood). Low-LG female, consumed less total fluid in general, and preferred 5% ethanol to water over the last three weeks of consumption compared to High-LG female. Maternal care didn't influence male ethanol consumption, preference, and total fluid consumption. While maternal care didn't alter sensitivity to acute ethanol-induced sedation during mid-adolescence, Low-LG male were more sensitive to ethanol-induced sedation than High-LG at all tested doses during late adolescence and adulthood. LG frequency also negatively correlated with sensitivity during late adolescence while the correlation approached ($p = 0.057$) significance in adults. Therefore, maternal care sex-dependently influences alcohol consumption, and age-dependently mediates male sensitivity to alcohol-induced sedation. This suggests that gonadal hormones play a role in the modulatory effects of maternal care on alcohol use. We are currently investigating the age-dependent effect on sensitivity in female, and also the mechanisms underlying these behavioral effects.

Disclosures: D.O. Popoola: None. **N.M. Cameron:** None.

Poster

777. Alcohol and Cannabis: Effects of Exposure During Adolescence

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Title: Voluntary exercise promotes resiliency to adolescent binge ethanol-induced reductions in adult brain serotonergic neuron markers

Authors: *R. P. VETRENO, T. J. WALTER, F. T. CREWS;
Sch. of Med., Univ. of North Carolina At Chapel Hill, Chapel Hill, NC

Abstract: Serotonergic neurons within the raphe nucleus are linked to the regulation of sleep, mood, and other functions that mature during adolescence. Binge drinking and alcohol abuse are common in humans adolescents, and we hypothesized that adolescent binge drinking might alter the development of the serotonergic leading to long-term changes in adult neurobiology. Using a Wistar rat model of adolescent intermittent ethanol treatment (AIE; 5.0 g/kg, i.g., 2-day on/2-day off from postnatal day [P] 25 to P55) followed by maturation to adulthood (P80), we discovered that AIE treatment reduced serotonin (5-HT)-immunoreactive (+IR) staining in the dorsal raphe nucleus, hypothalamus, and amygdala, but not the medial raphe nucleus. Western blot analysis revealed a a reduction in the 5-HT synthesizing enzyme tryptophan hydroxylase 2 as well as vesicular monoamine transporter 2, which packages 5-HT into synaptic vesicles, consistent with a loss of adult serotonergic neurons following AIE. Adolescent intermittent ethanol treatment increased the number of Iba-1+IR microglia and the microglial activation marker CD11b. To determine if microglial activation could recapitulate the effect of AIE on the serotonergic system, young adult rats (P70) were treated with lipopolysaccharide (1.0 mg/kg, i.p.), and 10 days latter 5-HT+IR was reduced similar to AIE treatment. Voluntary exercise during AIE and maturation into adulthood was found to prevent both the AIE-induced loss of 5-HT+IR in the dorsal raphe nucleus as well as the increases in Iba-1+IR and CD11b+IR. Together, these data suggest that adolescent binge ethanol treatment reduces serotonin in the young adult brain, possibly through a microglial mechanism. Voluntary exercise in the form of running wheel exposure promotes resilience to the deleterious effects of AIE treatment on the serotonergic system of the dorsal raphe nucleus. Long lasting reductions in brain serotonin following adolescent binge drinking could contribute to long-term changes in brain serotonin function. (Supported by the NADIA of the NIAAA)

Disclosures: **R.P. Vetreno:** None. **T.J. Walter:** None. **F.T. Crews:** None.

Poster

777. Alcohol and Cannabis: Effects of Exposure During Adolescence

Location: Hall A

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIAAA Grant AA017823-01 to LPS

Title: The ontogeny of ethanol aversion

Authors: ***J. SAALFIELD**, L. SPEAR;
Psychology, Binghamton Univ., Binghamton, NY

Abstract: Rodent models have been used to investigate factors potentially contributing to the increases in ethanol intake seen during adolescence. Such studies have determined adolescents to be less sensitive to many ethanol effects than adults, particularly those ethanol effects likely serving as cues to limit intake. While there is convincing evidence from both our laboratory and others that mid-adolescents are less sensitive to ethanol-induced conditioned taste aversion (CTA) than are adults, the precise ontogeny of this aversion is unknown. Given prior evidence showing discrete developmental windows within adolescence, the current experiment examined CTA to a range of ethanol doses across ages chosen to represent pre-adolescent/juvenile (Pre: P23-25); early adolescent (Early: P28-30), mid adolescent (mid: P35-37); late adolescent (late: P42-44); “emerging adult” (emerging: P52-54), and adult (P72-74) periods. In Exp. 1, pair-housed male Sprague-Dawley rats on ad-lib food and water were given 60 min access to chocolate Boost® while separated from their cagemates in their home cages, and injected intraperitoneally immediately thereafter with 0, 0.5, 1, 1.5, 2 or 2.5 g/kg ethanol. Testing occurred 48 hours later and consisted of an identical 60 min access period to the Boost® conditioned stimulus (CS). The results revealed two age groupings, with the 3 youngest ages (pre, early and mid) displaying an attenuated sensitivity to ethanol’s aversive properties relative to the 3 older age groups (late, emerging, adult), with CTAs not emerging until 2 g/kg and 1.5 g/kg, respectively. To assess whether the relative resistance to ethanol CTA seen in this study was related to the highly palatable nature of the Boost® solution, Exp.2 was conducted similarly except that supersaccharin was used as the CS, animals were 50% water deprived the day before training and testing to ensure adequate CS intake, and only doses of 0, 1.0, 1.5, and 2.0 g/kg were examined. Early adolescents showed no CTA at any dose, whereas pre-adolescents exhibited CTA only at 2.0 g/kg. Older animals were more sensitive to ethanol CTA, with the

mid, late and emerging groups displaying reduced sensitivity (1.5 g/kg) compared to adults (1.0 g/kg). In both studies, an attenuated sensitivity to the aversive properties of ethanol was evident in adolescents relative to adults, although more pronounced age differences were evident in water deprived animals than when a highly palatable CS was given to ad libitum animals. Overall, the attenuated sensitivity to the aversive properties of ethanol was most notable early in adolescence, with the enhanced aversive sensitivity of adults reached gradually thereafter.

Disclosures: J. Saalfield: None. **L. Spear:** None.

Poster

777. Alcohol and Cannabis: Effects of Exposure During Adolescence

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Program#/Poster#: 777.10/H42

Topic: C.17. Drugs of Abuse and Addiction

Support: K01 AA022475

U01 AA019967

F31 AA002843

R01 AA010983

Title: Binge-like alcohol exposure during adolescence disrupts dopaminergic neurotransmission in the adult prefrontal cortex

Authors: *H. TRANTHAM-DAVIDSON[1], S. CENTANNI[1], L. CHANDLER[2];
[1]Neurosci., [2]Med. Univ. of South Carolina, Charleston, SC

Abstract: The prefrontal cortex (PFC) is a brain region that is critically involved in cognitive function and inhibitory control. A, and adolescence represents a critical period of continued PFC development of this region that parallels the maturation of these its cognitive functions. This extended period of developmental plasticity is thought to renders the PFC, and its underlying circuitry, extremely especially vulnerable to environmental insult that, which may result in deficits that persist well intoproduce lasting changes that persist into adulthood. Alcohol drinking typically begins during adolescence when consumption of large quantities, in binge-like episodic patterns, is common. The present study investigated the effects of adolescent intermittent ethanol (AIE) exposure (post-natal day 28-42) by vapor inhalation on neurocircuitry in the adult medial PFC (mPFC). A primary function of dopamine (DA) in the PFC is to maximize the efficient

processing and transfer of information within the neurocircuitry that mediates decision-making. Dopamine (DA) innervation of the medial PFC (mPFC) peaks in early adolescence and then undergoes pruning and changes in DA receptor function during the transition to adulthood. These changes appear to play a critical role in the maturation of the executive function of the PFC. The present study investigated the effects of adolescent intermittent ethanol (AIE) exposure during post-natal days 28-42 by vapor inhalation on dopaminergic function in the prelimbic region of the adult PFC. Using Specifically,an adult acute slice preparation, we examined the functionality of pyramidal neuron DA receptors D1 and D2/D4 receptors of layer V pyramidal neuron in the prelimbic PFC was examined in the adult acute slice preparation. These studies revealed that AIE exposure resulted in a loss of D1 receptor modulation of pyramidal neuron intrinsic excitability and synaptic transmission, but had no effect on D2 or D4 modulationreceptor function. Interestingly, treatment with the D2 agonist eticlopride during AIE exposure period prevented the loss of D1 receptor function. In contrast, eticlopride treatment had no effect in the control air exposed rats. Taken together, these findings suggest demonstrate that binge-like alcohol exposure during early to mid adolescence compromises D1 receptor function, but co-administration of a DA D2 agonist during AIE exposure can protect against these deficits treatment with D2 agonists during alcohol exposure may be protective against these changes and result in and may prevent AIE induced deficits in the cognitive function of the PFC. improved cognitive outcomes.

Disclosures: H. Trantham-Davidson: None. **S. Centanni:** None. **L. Chandler:** None.

Poster

777. Alcohol and Cannabis: Effects of Exposure During Adolescence

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 777.11/H43

Topic: C.17. Drugs of Abuse and Addiction

Title: Biomolecularmarkers of impulsivity following adolescent alcohol-induced changes to the orbitofrontal cortex

Authors: C. R. SHORT, *M. S. MCMURRAY, J. D. ROITMAN;
Psychology, Univ. of Illinois At Chicago, Chicago, IL

Abstract: Adolescence is a developmental period that involves a significant increase in impulsive decisions and potential experimentation with drugs and alcohol. The prefrontal cortex (PFC) is thought to play a role in inhibiting impulsive choices. Because PFC undergoes continued development during adolescence, it may be sensitive to the effects of alcohol, altering

its developmental trajectory, thereby having long-term repercussions from casual abuse. In this study, a rodent model of alcohol abuse was used to investigate the effects of daily adolescent alcohol exposure on adult impulsivity and associated neurophysiology. Adolescent rats (10 per group) were injected (IP) with either a high dose of 3 mg/kg alcohol (EtOH) or saline (CONT), at the onset of the dark cycle from postnatal day 30-50. In adulthood, rats performed a probabilistic risk task. In this task, rats were presented with two levers: one lever constituting a safe option (1 pellet) and the other a risky option (3 or 0 sucrose pellets), based on a fixed probability for each session. The probability (12.5%, 33%, 50%, 67%, 75%) was varied between session to encourage risk-seeking or risk avoidance. Using this task, we found no behavioral differences between the CONT and EtOH exposed animals, with both showing generally risk-preferring behavior. Our lab has previously identified a regional impairment in the function of the orbitofrontal region of the PFC following alcohol consumption in adolescence. Thus, using qPCR, we examined mRNA levels in this region of genes thought to be involved in risk assessment, which included D1 and D2 dopaminergic receptors, α7 subunits of the nicotinic receptor, and muscarinic M1 receptors. Differential expression of these receptors has been shown to affect reward, motivation, and reinforcement in decision making and addiction studies. These findings will shed light onto the way in which adolescent alcohol intake affects decision making and in adulthood and will guide future research in finding novel treatments for the abuse of alcohol during this period.

Disclosures: **C.R. Short:** None. **M.S. McMurray:** None. **J.D. Roitman:** None.

Poster

777. Alcohol and Cannabis: Effects of Exposure During Adolescence

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIH Grant AA021233

Title: Aging increases alcohol sensitivity and eliminates circadian modulation of alcohol-induced behaviors in *Drosophila* melanogaster

Authors: *A. K. DENOBREGA, L. C. LYONS;
Biol. Science, Program of Neurosci., Florida State Univ., Tallahassee, FL

Abstract: Alcohol abuse and its physiological consequences in older adults is a serious problem given the rising elderly population and the increased physiological sensitivity to alcohol in aged

individuals. The patterns of alcohol consumption differ considerably between age groups as older individuals drink more frequently but consume fewer drinks at a time (Institute of Alcohol Studies, 2013) resulting in an underrepresentation of the extent of alcohol abuse in older adults. Although increased sensitivity to alcohol-induced motor and cognitive impairments can be observed in aged rodents as well as humans, little research has been done on the effects of acute alcohol in aged individuals (Novier et al., 2015). Compared to the neuronal complexity of mammalian systems, the simple circuitry of *Drosophila melanogaster* makes *Drosophila* a valuable model for identifying important factors and mechanisms in alcohol neurobiology (Guarnieri & Heberlein, 2003). Previously, we found that the circadian clock modulates the acute loss of motor control in flies using the loss-of-righting reflex (LoRR) assay. Flies exhibit a circadian rhythm in the LoRR with the greatest sensitivity to alcohol occurring from mid to late night (Van der Linde and Lyons, 2011). In the current research, we have extended these studies to investigate alcohol sensitivity and the role of the circadian clock in alcohol-induced behaviors in aged flies. We found that as flies age alcohol sensitivity increases and circadian regulation of alcohol sensitivity weakens. The circadian rhythm in LoRR remains significant at 10 days but disappears by 20 days of age. Interestingly, the behavior during the late subjective day when flies are normally the least sensitive to alcohol is most changed with aging. During the late subjective day, significantly less alcohol exposure is needed for LoRR in 10 day old flies compared to 3 day old flies with even shorter alcohol exposures necessary for 50% LoRR in 20 day old flies. Although age related changes in alcohol sensitivity may also be observed during the late night when flies are most sensitive to alcohol, these changes are smaller in magnitude compared to the late subjective day. These results suggest the hypothesis that the circadian clock phase specifically buffers the effects of alcohol exposure and that this influence on alcohol-induced behaviors is diminished with aging. These behavioral studies demonstrate that *Drosophila melanogaster* is a practical model system for studying the effects of alcohol in aging populations and for investigating the potential protective aspect of the circadian clock in acute alcohol use.

Disclosures: **A.K. Denobrega:** None. **L.C. Lyons:** None.

Poster

777. Alcohol and Cannabis: Effects of Exposure During Adolescence

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 777.13/H45

Topic: C.17. Drugs of Abuse and Addiction

Support: NIH Grant P50 AA017823

Title: Adolescent ethanol exposure leads to durable changes in HPA axis sensitivity to an immune stimulus at adulthood

Authors: *A. S. VORE, T. L. DOREMUS-FITZWATER, A. GANO, J. PANICCIA, T. DEAK; Binghamton Univ., Binghamton, NY

Abstract: Adolescent alcohol use comprises a significant public health concern and is often characterized by binge-like consumption patterns. While ethanol exposure in adulthood has been shown to alter several aspects of the stress response, including the Hypothalamic-Pituitary-Adrenal (Axis), few studies have examined whether binge-like ethanol exposure during adolescence results in enduring changes in HPA axis sensitivity that could persist into adulthood. In the present series of studies, therefore, male adolescent Sprague-Dawley rats were given intragastric (i.g.) intubations of ethanol (4 g/kg) or vehicle once per day for 3 consecutive days, beginning on postnatal day (P) 30 (± 1). This binge exposure was immediately followed by a 2-day period of rest/withdrawal. Rats then received one more 3-day cycle of ethanol exposure and were subsequently allowed to age normally until reaching adulthood. At P73 (± 2), separate groups of ethanol- and vehicle-exposed rats received 1 of 3 distinct stress challenges to probe HPA axis sensitivity across unique stress modalities: (i) In Exp. 1, animals were given an acute challenge of 2.5 g/kg ethanol (intraperitoneally; i.p.); (ii) In Exp. 2, rats received an acute injection of a moderate dose (50 μg/kg) of lipopolysaccharide (LPS); and (iii) In Exp. 3, a third cohort of adolescent-exposed rats was challenged with 60 min of restraint. In all experiments, a time course of tail blood samples were collected for later assessment corticosterone (CORT) concentrations, as well as other blood measures. As expected, all 3 stress challenges led to a time-dependent surge in CORT release. Whereas 2 of the adult challenges (ethanol and restraint) showed a trend for increased sensitivity following adolescent ethanol exposure, acute administration of LPS resulted in the opposite pattern: a decrease in the CORT response. Gene expression analyses of cytokines (IL-6, IL-1, and TNF alpha) from the white blood cell layer of fractionated whole blood using RT-PCR revealed that adolescent ethanol exposure led to attenuated LPS-induced increases in cytokines, with this reduction significant for IL-6 expression. These findings suggest that adolescent ethanol exposure may cause lasting alterations in HPA axis sensitivity that (a) persist into adulthood and (b) may vary depending on the nature of the challenge incurred during adulthood; and (c) that adolescent ethanol exposure may produce enduring changes in processing of antigen by the immune system and/or neuroimmune function. Future studies identifying the cellular mechanisms underlying these effects are currently under way.

Disclosures: A.S. Vore: None. **T.L. Doremus-Fitzwater:** None. **A. Gano:** None. **J. Paniccia:** None. **T. Deak:** None.

Poster

777. Alcohol and Cannabis: Effects of Exposure During Adolescence

Location: Hall A

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIH Grant AA021013

NSF Grant HRD 0450339

Title: The effect of adolescent binge drinking on oxidative stress in the prefrontal cortex

Authors: *W. VARGAS, A. DAVE, H. N. RICHARDSON;
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Abstract: Underage binge drinking is associated with various harmful health effects and social problems. Moreover, alcohol is the most commonly used and abused drug by adolescents. During adolescence, brain regions such as the prefrontal cortex (PFC) are still developing and thus may be more vulnerable to potentially toxic substances like alcohol. Extremely high doses of alcohol administered to animals are known to induce oxidative stress, which is an imbalance of oxidants and antioxidants in an aerobic system. The objective of the present study was to determine the effect of voluntary binge drinking on oxidative stress in gray and white matter of the PFC in young animals. Adolescent male and female Wistar rats were exposed to two weeks (postnatal days 28-42) of operant binge alcohol self-administration. After the end of the binge treatment period, brains were collected and the PFC was processed for oxidative stress assays. The 2, 7-Dicholorofluorescein and BCA protein assays were used to determine reactive oxidative species concentrations as an index of oxidative stress. Preliminary results suggest sex differences in oxidative stress levels in the PFC after alcohol, with a trend of higher levels in males compared to females. These data suggest differential sensitivity of the male and female PFC to alcohol early in adolescence in rats.

Disclosures: W. Vargas: None. **A. Dave:** None. **H.N. Richardson:** None.

Poster

777. Alcohol and Cannabis: Effects of Exposure During Adolescence

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Support: NIH-AA-019971 to SCP

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Title: Adolescent alcohol exposure suppresses the CREB signaling system in the rat amygdala during adulthood

Authors: H. ZHANG[1,2,3], D. KOKARE[1,3], E. J. KYZAR[1,2,3], T. TEPPEN[1,2,3], *S. C. PANDEY[1,2,3];
[1]Dept Psychiatry, Univ. of Illinois at Chicago, Chicago, IL; [2]Jesse Brown VA Med. Ctr., Chicago, IL; [3]Ctr. for Alcohol Res. in Epigenetics, Chicago, IL

Abstract: The cAMP-responsive element binding protein (CREB) transcription factor in the amygdala has been shown to be involved in anxiety-like and alcohol drinking behaviors. In addition, it has been shown that withdrawal from chronic ethanol treatment reduces CREB phosphorylation and CBP expression in the amygdala of adult rats and this is associated with the development of anxiety-like behaviors. In the present study, we assessed the effect of adolescent intermittent n-saline (AIS) or intermittent ethanol (AIE) exposure on CREB phosphorylation and expression of CBP and p300 in the amygdaloid structures of rats in adulthood. Rats were exposed to intermittent ethanol treatment (2 g/kg, intraperitoneal) during post-natal days (PND) 28-41, with one injection per day for two consecutive days. This was followed by 2 days without ethanol treatment for a total of 4 cycles. The rats were left undisturbed in their home cage until PND 92 without additional ethanol exposure. At this time point, brains were dissected to measure CREB and phosphorylated CREB (pCREB) protein levels and protein and mRNA levels of CBP and p300 in amygdala of AIE and AIS exposed adult rats. It was found that CREB and pCREB protein levels and mRNA and protein levels of CBP and p300 were significantly reduced in the amygdala of AIE adult as compared with AIS adult rats. While AIE rats showed a significant reduction in protein levels in the central (CeA) and medial nucleus of amygdala (MeA), protein levels of these molecular markers in the basolateral amygdala (BLA) did not change. These results indicate that AIE exposure reduces CREB signaling and related co-factors CBP and p300 expression in the CeA and MeA during adulthood that may be associated with AIE-induced anxiety and alcohol intake as previously reported by our laboratory.

Disclosures: H. Zhang: None. **D. Kokare:** None. **E.J. Kyzar:** None. **T. Teppen:** None. **S.C. Pandey:** None.

Poster

777. Alcohol and Cannabis: Effects of Exposure During Adolescence

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIH Grant AA020022

Title: Adolescent intermittent ethanol alters oligodendrocytes and myelin in the prefrontal cortex of adult male rats

Authors: *W. LIU, F. T. CREWS;
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Abstract: Prefrontal cortex (PFC) and white matter development parallels maturation of cognitive control, executive functions and working memory. Binge drinking is common in adolescent humans. The current study examined the effect of adolescent intermittent binge ethanol (AIE) compared with water controls on oligodendrocytes and myelin in the prelimbic (PrL) subregion of the prefrontal cortex of adult male rats. Timed-pregnant dams (E17) were allowed to acclimate to our vivarium on (P1), litters were culled to 10 pups, weaned on P21, male weight matched and pair-housed. Two groups were treated with ethanol (AIE, 5g/kg/day, i.g., P25-P55; 2 days alcohol, 2 days off) and another two groups were given water as controls, control and AIE groups were sacrificed at P57 or P95. The impact of AIE on white matter maturation was investigated using immunohistochemistry in PrL for the following markers of oligodendrocytes and myelin; NG2 (a marker of oligodendrogenesis progenitor cells, OPCs), Olig2 (OPCs and mature oligodendrocytes), PDGF Rα (oligodendrocyte progenitor cells), Olig1 (nuclear, OPC and immature oligodendrocyte), MBP (hydrophilic myelin basic protein), dMBP (degraded myelin basic protein), MOP (Myelin oligodendrocyte glycoprotein) and PLP (highly hydrophobic transmembrane proteolipid protein). Multiple markers showed age-related changes consistent with maturation, For example, between P57 and P95, there was age-related decrease in NG2+IR (37%, $p<0.01$), Olig1+IR (30%, $p<0.05$), Olig2+IR (18%, $p<0.05$), dMBP+IR (76%, $p<0.001$) and MOG+IR (50%, $p<0.01$) expression, that contrasts with an age-related increase in PLP+IR (177%, $p<0.05$) in control group. AIE did not change many oligodendrocyte markers at P57, but did decrease PGDF Rα+IR, MBP+IR, dMBP+IR and MOG+IR at P57. At P95, AIE increased Olig2+IR (21%, $p<0.05$), MOG+IR (45%, $p<0.05$) and PLP+IR expression (151%, $p<0.01$) in the PrL, and dMBP+IR remained decreased at P95. These data are consistent with AIE indicate altering oligodendrocytes and myelin maturation leading to persistent changes in PFC. (Funded by the NADIA from NIAAA).

Disclosures: W. Liu: None. **F.T. Crews:** None.

Poster

777. Alcohol and Cannabis: Effects of Exposure During Adolescence

Location: Hall A

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Support: AA019431

AA021099-S1 (JBD)

AA021099

AA014106 (DPF)

Diagnostic Neurology and Wound Care Center

Center for Biomolecular Imaging

Translational Science Institute WFSOM

Title: Disruption of early stage resting state activity as a function of alcohol consumption in nonhuman primates: an MEG study

Authors: *J. R. STAPLETON-KOTLOSKI[1], J. A. ROWLAND[2,4], A. T. DAVENPORT[3], P. M. EPPERLY[3], D. P. FRIEDMAN[3], D. W. GODWIN[2], J. B. DAUNAIS[3];
[2]Neurobio. & Anat., [3]Physiol. & Pharmacol., [1]Wake Forest Univ. Sch. of Med., Winston Salem, NC; [4]W.G. "Bill" Hefner VAMC, Salisbury, NC

Abstract: Chronic alcoholism is characterized by structural damage and cognitive deficits, but when these manifest is unclear. Here we used resting state (RS) MEG to image two cohorts of nonhuman primates (NHPs) following a chronic EtOH exposure paradigm. The first study was a cross-sectional comparison of a group of vervet monkeys that had chronically self-administered EtOH (n=7) or maltodextrose (n=3) under identical operant conditions (3 month induction + 12 months daily access with average daily EtOH intakes of 1.1-3.1 g/kg). RS MEG data were beamformed with synthetic aperture magnetometry (SAM) and source series were extracted for peaks and selected ROIs. Chronic EtOH altered precuneus RS activity in an intake-dependent manner such that non-heavy drinkers exhibited similar SAM z-scores to control animals as compared to heavy drinkers. RS source series activity in chronically drinking vervets demonstrated clear power spectral reductions in all frequencies from 0-80 Hz in anterior cingulate (ACC), dorsolateral prefrontal cortex (DLPFC), hippocampus (HPC), and vermis

relative to controls. These robust decreases were detected after chronic, daily access for 15 months so it was not possible to determine when the reductions began. Data from an ongoing study in which rhesus monkeys (n=5) self-administered EtOH under identical operant conditions as the vervets described above found that RS activity is altered in a rate-dependent manner immediately after a 3-month induction phase during which all EtOH animals consume identical g/kg doses of EtOH. Relative to the naïve pre-induction RS scans, power spectral densities revealed increased power in left DLPFC, left medial orbitofrontal cortex, and bilateral ACC. While power increased for all animals in frontal regions, there was differential sensitivity in more caudal regions such as HPC or vermis such that the slowest drinker displayed increased power while the fastest drinker displayed decreased power. The link between RS activity and drinking rate is important since early drinking typographies (i.e., 'gulping' vs 'sipping') are highly predictive of subsequent daily EtOH intake in NHPs (Grant et al., 2008). Finally, other regions such as bilateral substantia nigra and amygdala exhibited decreased power following EtOH. Collectively, these data suggest that in several brain areas implicated in alcoholism functional changes occur very early in the drinking history, are regionally selective, and likely precede structural changes. RS alterations early in the drinking history may also be a non-invasive biomarker predictive of a heavy drinking phenotype.

Disclosures: J.R. Stapleton-Kotloski: None. **J.A. Rowland:** None. **A.T. Davenport:** None. **P.M. Epperly:** None. **D.P. Friedman:** None. **D.W. Godwin:** None. **J.B. Daunais:** None.

Poster

777. Alcohol and Cannabis: Effects of Exposure During Adolescence

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIH 1R03 DA027457

Title: FAAH moderates neurocognitive effects of cannabis use in youth

Authors: *K. M. LISDAHL;
Psychology, Univ. of Wisconsin-Milwaukee, Milwaukee, WI

Abstract: Intro: The last two decades there has been a rise in adolescent cannabis use, with 6.5% of 12th graders reporting daily use (Johnston et al., 2013). Adolescence is a sensitive period that involves significant neurodevelopmental changes in both gray and white matter (Giedd et al., 1996; Sowell et al., 2004) and drug exposure during these years is if particular concern.

Therefore, it continues to be a top public health priority to characterize the public health impact of cannabis exposure and to identify potential at-risk groups for greater neurocognitive deficits. Genetic differences may place individuals at increased risk for these cognitive effects. Two candidate genes are *FAAH*, which regulates the endogenous cannabinoid anadamide, and the CB1 receptor (*CNR1*) (Ho & Hillard, 2005). It was hypothesized that regular cannabis users who are also carriers of the *FAAH* A genotype, related to diminished endocannabinoid signaling, will demonstrate greater neurocognitive and sleep consequences. **Methods**. As part of the parent study, cognitive, substance use, sleep quality, and DNA data was collected from 83 youth (ages 18-25), including 38 regular cannabis users and 45 healthy controls. SNP genotyping was obtained for *FAAH* (rs324420) and *CNR1* (rs2180619). Exclusion criteria included independent psychiatric disorders, neurologic or major medical disorders, left-handedness, non-English speakers, history of prenatal drug exposure, intellectual disability, reading ability <80 Standard score, significant other drug use (>25 times in lifetime). **Results.** We will present a series of studies examining the independent and interactive effects of cannabis and *FAAH* genotype on neurocognition and sleep. Main effects of cannabis included reduced orbitofrontal and parietal volume, reduced prefrontal gyrification, poorer frontolimbic white matter integrity, worse problem solving/set shifting and psychomotor speed, and poorer sleep quality (*p*'s<.05). *FAAH* genotype significantly moderated the effects of cannabis on verbal retention, working memory, orbitofrontal morphology, and frontolimbic white matter integrity (*p*'s<.05). **Discussion**. These gene-by-cannabis use interactions may explain inconsistency in the literature. Other clinical and policy implications will be discussed.

Disclosures: K.M. Lisdahl: None.

Poster

777. Alcohol and Cannabis: Effects of Exposure During Adolescence

Location: Hall A

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIH R01 DA030344

Title: Onset-specific effects of regular cannabis use on brain functional systems

Authors: *F. FILBEY[1], V. MISHRA[2];
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Abstract: Graph theory models propose that brain regions have a pattern of functional connections that form a brain functional system. Thus, graph theory provides a more holistic understanding of brain function relative to regional activations (Bullmore & Sporns 2009). Such models have shown that functional systems are sensitive to developmental/aging effects as well as exposure to substances (e.g., decreases in modularity, efficiency). The goal of this study was to determine the interaction between these two factors on graph metrics. To that end, 128 regular cannabis users (age range: 31±7 years) were scanned using resting state functional MRI (rsfMRI). After routine preprocessing of all rsfMRI images (e.g: motion correction, band-pass filtering, etc), nodes of the network (graph) were derived by registering each brain to AAL atlas yielding 45 regions in each hemisphere. The mean time series for each region was calculated by averaging the time series of all the voxels within each region. Further, a symmetric correlation matrix of size 90x90 was generated from Pearson correlation coefficients between each pair of nodes, for each subject. Each correlation matrix was further converted into a weighted network (weights being the correlation between any two nodes) and binary network (weights of the non-zero edges in the weighted graph equated to 1). Each of such binary and weighted networks was explored for two sets of network properties: global network metrics, yielding information about the topological brain properties such as small-worldness, path length, clustering coefficient, hierarchy, modularity, efficiency etc and regional nodal metrics such as nodal efficiency, betweenness, nodal efficiency, cluster and nodal participant etc. The network properties thus obtained were compared across the cannabis users to see the difference in the brain organization due to early and late onset of regular use of cannabis. Our findings suggest that effects on functional systems as measured by graph metrics are moderated by age of onset of regular use, particularly in the default mode network (DMN), fronto-parietal network (FPN; cognitive control), salience network (SN; directed attention) and subcortical (limbic/reward) network. These findings demonstrate the presence of observable effects on brain functional systems across the lifespan that are unique to the age of onset.

Disclosures: **F. Filbey:** None. **V. Mishra:** None.

Poster

777. Alcohol and Cannabis: Effects of Exposure During Adolescence

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIDA

ORDCF

Title: Comparing effects of alcohol and marijuana: An n-back fmri study in young adults

Authors: A. BYRON-ALHASSAN, T. HATCHARD, O. MIODUSZEWSKI, *A. SMITH; Univ. of Ottawa, Ottawa, ON, Canada

Abstract: Alcohol and marijuana are the most commonly used drugs during adolescence. Within the past five years, alcohol usage has declined while marijuana usage has increased. Given this increase in marijuana use among teenagers, and the potential combination of using both alcohol and marijuana during this time when brain maturation is so vital, it is critical to understand the neurophysiological impacts of both drugs on the teen brain. The optimization of brain development can be monitored by proficiency in working memory. As usage and public opinion of drug use is often a result of the perceived risk of the substance, a comparison of the performance and neurophysiological impact of each drug during a working memory task will be of considerable relevance. The purpose of the present study was to compare the effects of alcohol with those of marijuana, on a functional magnetic resonance imaging (fMRI) working memory task, in adolescent users. **Methods** Participants were recruited from the Ottawa Prenatal Prospective Study. Ten marijuana users were compared with 14 non-users and 17 alcohol users were compared with 11 non-users. Each participant attended one imaging session on a 1.5 T Siemens Magnetom Symphony MR scanner for whole brain BOLD fMRI. A 2-back letter n-back task was used. For both drugs, BOLD activations during the working memory task, and performance (reaction time and errors) were compared to the respective control group of non-users using SMP8. **Results/Conclusions** No significant differences in performance were found between groups. fMRI analyses revealed significantly more activity in both drug groups compared to controls but the areas of increased activity during working memory were different for the 2 drugs. Alcohol users had significantly more activity in the cingulate gyrus and the right caudate nucleus, while the marijuana users engaged the middle temporal gyrus and cerebellum significantly more than controls. These findings suggest that, although both substances produce a need for additional resources to maintain successful performance, the mechanism by which they function differs. This additionally implies that, especially in the developing brain, use of both marijuana and alcohol would cause more widespread negative effects on neural processing.

Disclosures: A. Byron-Alhassan: None. **T. Hatchard:** None. **O. Mioduszewski:** None. **A. Smith:** None.

Poster

778. Cocaine: Cellular and Synaptic Studies

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Topic: C.17. Drugs of Abuse and Addiction

Support: TL1 TR000061

UL1 TR000062

T32 GM008716

P50 DA015369

R01 DA012513

F30 DA038893

Title: Extinguished environment elicits transient synaptic potentiation in the accumbens shell

Authors: *D. ROBERTS-WOLFE[1], C. GIPSON[1], A. MOTTS[2], A. SMITH[1], K. WISCHUSEN[2], M. SCOFIELD[1], P. KALIVAS[1];
[1]Neurosci., Med. Univ. of South Carolina, Charleston, SC; [2]Col. of Charleston, Charleston, SC

Abstract: Discovering mechanisms underlying inhibition of drug seeking is critical to developing new therapies for substance use disorders. Extinction training consists of animals repeatedly receiving no reinforcement for pressing a lever formerly paired with cocaine infusions. Animals successfully inhibit drug seeking when returned to the extinguished context (the operant chamber in which they underwent extinction training). This inhibition requires neuronal activity in nucleus accumbens (NA) shell and its prefrontal (infralimbic) input. Transient synaptic potentiation (tSP) in accumbens medium spiny neurons (MSNs) is a physiological correlate of behaviors requiring glutamatergic inputs into nucleus accumbens. For example, cue-induced reinstatement of drug seeking is associated with a tSP (rapid increases in AMPA:NMDA ratio and dendritic spine head diameter that normalize by the end of the reinstatement session) that requires prefrontal inputs and activation of matrix metalloproteinases (MMPs 2 and 9). As tSP is associated with behavior relying on glutamate in nucleus accumbens, and glutamate in NA shell is necessary for inhibiting drug seeking in an extinguished context, we hypothesize that exposure to an extinguished context will induce tSP in NA shell. Following 10 days of cue-paired cocaine self-administration, animals underwent 2-3 weeks of either extinction training in the same context (but without discrete cues) or home-cage abstinence. Animals were sacrificed after returning for 15 minutes to the context in which they had undergone self-administration (with or without extinction training), or sacrificed without re-exposure to the context. We used whole cell patch clamp electrophysiology to examine AMPA:NMDA ratio and diolistic labeling to image dendritic spines. Exposure to the extinguished context induced tSP in NA shell. AMPA:NMDA ratios were increased in animals re-exposed to the extinguished context relative to extinguished animals not re-exposed. Spine morphology was not affected by

re-exposure to an extinguished context. No changes were noted in NA shell as a result of cocaine self-administration or extinction training alone. The fact that 15 min of exposure to the extinguished environment increased AMPA:NMDA, but did not change spine morphology differs from tSP characterized during reinstatement in NA core, and suggests dissociable mechanisms underlying these two common measures of synaptic plasticity. Future studies will examine the role of MMPs and infralimbic inputs on tSP induced in the NAshell by an extinguished environment.

Disclosures: **D. Roberts-Wolfe:** None. **C. Gipson:** None. **A. Motts:** None. **A. Smith:** None. **K. Wischusen:** None. **M. Scofield:** None. **P. Kalivas:** None.

Poster

778. Cocaine: Cellular and Synaptic Studies

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIDA-IRP, NIH/DHHS

Title: Elucidating the effects of atypical dopamine uptake inhibitors on the phasic release of dopamine in mice

Authors: J. KEIGHRON, *A. H. NEWMAN, G. TANDA;
NIDA-IRP, Baltimore, MD

Abstract: Atypical dopamine uptake inhibitors, such as JHW 007, have low potential for abuse and may lead to critical discoveries in the development of treatments for psychostimulant abuse. These compounds are known to bind to the dopamine transporter with high affinity and block the pharmacological and behavioral effects of stimulant drugs of abuse, such as cocaine and methamphetamine. The objectives of this study are to explore the effects of JHW 007 and other typical and atypical dopamine uptake inhibitors on the phasic release of dopamine. We would also like to determine how these effects correlate with the previously reported behavioral and tonic dopamine level data. Fast scan cyclic voltammetry (FSCV) is an electrochemical method that allows for the study of the phasic release of dopamine both *in vivo* and *ex vivo*. In this study, phasic dopamine release in the striatum of male Swiss-Webster mice was followed both prior to, and for several hours after administration of cocaine or JHW 007 with doses ranging from 0.3 mg/kg to 32 mg/kg. This allowed us to study the effects of both drugs on the intensity, duration, and effective clearance of dopamine released during phasic events as the effects of each drug

developed. Initial results indicate that both typical and atypical inhibitors effect phasic dopamine release by two mechanisms, increasing the amount of dopamine release per event, and decreasing the rate of clearance of dopamine from the intercellular space as evident by the changes in the intensity and duration of events when inhibitors are present. When cocaine is administered these mechanisms are affected in a dose dependent manner. However, atypical inhibitors such as JHW 007 do not produce the same magnitude of effect at similar doses, and may act on these two mechanisms at different times, causing the apparent shift in the dose response curve previously reported with microdialysis. In summary, our results help provide a broader view of the role of JHW 007 and other atypical dopamine uptake inhibitors in potential treatments for stimulant abuse by elucidating the mechanisms involved in the phasic release of dopamine.

Disclosures: J. Keighron: None. **A.H. Newman:** None. **G. Tanda:** None.

Poster

778. Cocaine: Cellular and Synaptic Studies

Location: Hall A

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Program#/Poster#: 778.03/I7

Topic: C.17. Drugs of Abuse and Addiction

Support: DA005010286505

Title: Beta-arrestin 1 dependent regulation of cocaine self-administration in mice

Authors: *N. MITTAL[1], A. MINASAYAN[2], T. SCHALLERT[3], C. J. EVANS[2], W. M. WALWYN[2];
[1]Univ. of Texas At Austin, Austin, TX; [2]UCLA, Los Angeles, CA; [3]Univ. of Texas at Austin, Austin, TX

Abstract: Prolonged use of cocaine results in long lasting synaptic changes in the mesolimbic reward centers. Identification of substrates that are responsible for the induction and maintenance of such plasticity may help provide novel therapeutic targets for the treatment of substance abuse and relapse. Cocaine self-administration has been shown to abolish long term depression (LTD) in the bed nucleus of the stria terminalis (BNST), which can be rescued by blockade of the NR2B subunit of the N-Methyl-D-aspartate receptor (NMDAR). Studies have shown a similar blockade of LTD in the NAc following cocaine self-administration. We have previously shown a role of the scaffolding protein, β-arrestin 1, in modulating GPCR expression and function by regulating pathways responsible for receptor trafficking onto the cell membrane. Therefore, we

hypothesized that β- arrestin 1 may be involved in regulating cocaine-induced changes in NMDAR expression and function. We trained mice lacking β-arrestin 1 to self-administer cocaine, and measured synaptic activity from medium spiny neurons (MSNs) in the shell of the NAc, before and after cocaine self-administration. We found that mice lacking β-arrestin 1 had increased basal AMPA to NMDA ratios in the NAc as compared to the wild-type mice. Moreover, the β-arrestin 1 knockout mice were slower in both acquiring, and extinguishing cocaine self-administration. Furthermore, unlike wild-type mice, the knockout mice did not show an increase in NR2B receptor expression after the acquisition of cocaine self-administration. These findings identify a, previously unknown, role of β-arrestin 1 in regulating NMDAR function following cocaine self-administration.

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Poster

778. Cocaine: Cellular and Synaptic Studies

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NARSAD

Title: Examining the role of toll-like receptor 4 on nucleus accumbens synaptic physiology and drug reward behavior

Authors: *D. T. KASHIMA[1], B. A. GRUETER[2];
[2]Anesthesiol. Res., [1]Vanderbilt Univ., Nashville, TN

Abstract: Drug abuse and addiction remain significant problems in society. Drugs of abuse alter the nucleus accumbens (NAc) physiology suggesting it plays a role in a final common pathway for dependence/addiction. The NAc is made up of two types of medium spiny projection neurons (MSNs) that differentially modulate reward behavior. Neuron-mediated mechanisms of change at excitatory synapses within the NAc in response to drug experience are well-studied. However, growing evidence suggests the involvement of the brain's innate immune system in modulating reward behavior and synaptic physiology. Previous studies demonstrated that pharmacologic manipulation of toll-like receptor 4 (TLR4), a pattern-recognition molecule of the innate immune

system, attenuates cocaine-reward learning. In the brain, TLR4 is primarily associated with microglia. Microglia are phagocytes with the ability to regulate synaptic physiology through 1) physical removal of synapses during development, 2) responses to certain forms of injury, and 3) secretion of chemical factors known to mediate homeostatic plasticity. Despite these observations, mechanistic examination of how the innate immune system alters NAc synaptic physiology in relation to drug-reward behavior has not been demonstrated. We performed behavioral assays as well as cell-type specific electrophysiology on wild type and TLR4 knockout mice. We show that TLR4 knockout mice exhibit altered NAc synaptic plasticity and express an attenuation in cocaine-mediated reward learning. Additionally, we find that pharmacologic agonism of TLR4 modifies NAc MSN synaptic plasticity. These results suggest that TLR4 and the immune system may directly affect synaptic physiology to alter reward behavior.

Disclosures: D.T. Kashima: None. **B.A. Grueter:** None.

Poster

778. Cocaine: Cellular and Synaptic Studies

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Topic: C.17. Drugs of Abuse and Addiction

Support: DA012513

Title: Cell type specific dysregulation of GABAergic plasticity in the Ventral Pallidum after extinction from cocaine self administration

Authors: *D. NEUHOFER[1], Y. KUPCHIK[2], P. KALIVAS[1];
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Abstract: The Ventral pallidum (VP) is the main target of the mesolimbic indirect pathway and as such integrates motivational and sensory information. It has been demonstrated that the projection from the nucleus accumbens (NAc) to the VP regulates the reinstatement of cocaine-seeking, a process which depends on normal activation of mu opioid receptors. Indeed, NAc-VP GABAergic synapses of drug-naïve animals undergo a form of presynaptic long-term depression (LTD) that is mu opioid receptor dependent. This form of plasticity is abolished in cocaine-extinguished rats due to tonic saturation of mu opioid receptors. Classically it is thought that the output from the NAc to the VP is composed exclusively of axons of medium spiny neurons

(MSNs) expressing the D2 dopamine receptor (D2-MSNs). However, we have recently shown that the VP receives significant input from D1-MSNs and that projections from the NAc to VP contain D1 mRNA, questioning this strict segregation. Here we examine whether both accumbal inputs to the VP express electrically-induced LTD and the effect of extinction of cocaine-seeking behavior on each input. Using Cre dependent expression of ChR2 in either D1 or D2 MSNs we demonstrate that while both inputs exhibit LTD in drug-naïve mice, the elimination of GABAergic LTD in cocaine-extinguished mice described previously is cell type specific. While LTD can still be elicited in D1 MSN input to the VP of cocaine extinguished mice, LTD in D2 MSN terminals is abolished. This differential effect of cocaine on plasticity may be explained by differences in signaling pathways and further research is required to identify the relevance of each of these VP afferents to the reinstatement of cocaine seeking behavior.

Disclosures: **D. Neuhofer:** None. **Y. Kupchik:** None. **P. Kalivas:** None.

Poster

778. Cocaine: Cellular and Synaptic Studies

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Topic: C.17. Drugs of Abuse and Addiction

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Title: Inherent individual differences in dopamine release are associated with variability in subsequent cocaine consumption

Authors: *J. K. SHAW, R. A. ESPAÑA;
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Abstract: The mesolimbic dopamine (DA) system is heavily implicated in the onset and maintenance of cocaine use and variability within this pathway is believed to underlie individual differences in vulnerability to the development of cocaine abuse and addiction. Previous work has demonstrated that rats classified as high responders to novelty acquire cocaine self-administration more readily and are characterized by both greater DA-ergic storage capacity and cocaine-induced uptake-inhibition than those identified as low responders. Despite this evidence, the direct relationship between DA neurotransmission and individual differences in cocaine self-administration has not yet been fully elucidated. To determine the relative contributions of DA release and uptake to vulnerability to use cocaine, we measured baseline DA release and uptake dynamics in the striatum of anesthetized rats using fast scan cyclic voltammetry prior to any

behavioral testing. Following recovery, the rats were provided access to cocaine-associated levers and the time to acquire, consumption of, and motivation for cocaine using fixed ratio-1 and within-subject threshold schedules of reinforcement was measured. Preliminary results suggest a strong relationship between baseline DA release and cocaine consumption while uptake did not appear to be strongly associated with any behavioral measure, potentially implicating DA reserve pools in vulnerability to cocaine use disorders. These data suggest that individual differences in cocaine self-administration may be associated with inherent variability in the mesolimbic DA system. The current findings may aid in further development of targeted pharmacotherapies to treat cocaine addiction.

Disclosures: J.K. Shaw: None. **R.A. España:** None.

Poster

778. Cocaine: Cellular and Synaptic Studies

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Topic: C.17. Drugs of Abuse and Addiction

Title: PCAF regulates the acetylation of Sigma-1 receptor chaperones

Authors: *Y. YASUI[1], T.-P. SU[2];
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Abstract: Sigma-1 receptors (Sig-1Rs) are endoplasmic reticulum (ER) chaperon proteins that are implicated in various neurological disorders. Sig-1Rs have received attention because of the specific involvement in drug abuse. Since antagonizing Sig-1Rs diminishes cocaine-induced behavioral responses, Sig-1Rs are expected to be a potential therapeutic target of cocaine abuse. Sig-1Rs predominantly reside at the mitochondria-apposing ER subdomain (the mitochondria-associated ER membrane, MAM) but can translocate to other compartments of the cell under stimulation with cocaine. We previously showed that cocaine-induced translocation of Sig-1Rs, which intensifies the Sig-1R interaction with Kv1.2 potassium channel, plays a substantial role in behavioral and neuronal responses to cocaine in mice. Thus, the dynamic shift of the subcellular distribution is a critical step for Sig-1Rs to execute their functions at remote sites other than the MAM. However, the detailed mechanism on how the translocation is initiated is largely unknown. We found that Sig-1Rs interact with lysine acetyltransferases, p300/CBP-associated factor (PCAF) and GCN5. The interaction between Sig-1Rs and PCAF possibly occurs at the ER and the ER-Golgi intermediate compartment, and is intensified with cocaine treatment. It has been reported that acetylation of membrane proteins in the ER lumen regulates the protein

translocation at the early secretory segment of the translocation pathway. We therefore hypothesized that PCAF and GCN5 may acetylate Sig-1Rs and the acetylation of Sig-1Rs may be related to the Sig-1R's translocation. We found that the acetylation level of Sig-1Rs is increased by overexpression of PCAF and decreased by knockdown of PCAF. We also found that cocaine intensifies the interaction between PCAF and Sig-1Rs. However, paradoxically, cocaine does not affect the acetylation level of Sig-1Rs. We examined whether the PCAF expression level may affect the subcellular distribution of Sig-1Rs by density gradient centrifugation, and found that overexpression or knockdown of PCAF did not significantly changed the distribution pattern of Sig-1Rs. Together, our data show that Sig-1Rs are acetylated and PCAF regulates the Sig-1R acetylation level. Although cocaine affects the interaction between Sig-1Rs and PCAF, PCAF-induced acetylation of Sig-1Rs may not be the underlying mechanism whereby cocaine causes the translocation of Sig-1Rs.

Disclosures: Y. Yasui: None. **T. Su:** None.

Poster

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Topic: C.17. Drugs of Abuse and Addiction

Support: R00DA031699

Title: Synapse-specific deconstruction of endocannabinoid signaling in the nucleus accumbens shell

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Abstract: Aberrant glutamatergic transmission within the nucleus accumbens shell (NAcSh) is heavily implicated in the development and reinstatement of drug-induced addiction-like behaviors. Integration of glutamatergic input from the medial prefrontal cortex (mPFC) and basolateral amygdala (BLA) by NAcSh medium spiny neurons is thought to encode stimulus salience and direct associative learning processes. Moreover, long-lasting adaptations at these synapses have been repeatedly linked to drug self-administration and the incubation of drug craving in rodent models of addiction. Extensive investigation has highlighted NAcSh post-synaptic plasticity mechanisms as highly-penetrant molecular mediators of maladaptive

associative-learning pathologies. However, less is known regarding presynaptic regulatory mechanisms and their contribution to drug-induced remodeling of reward circuitry function. Presynaptic regulation in the NAc via endocannabinoids (eCBs) and the cannabinoid type-1 receptors have been correlated with non-contingent drug exposure and self-administration behaviors. However, how the eCB system functions at discrete synapses remains unknown. Here, we utilize whole-cell electrophysiology, transgenic D1tdTom marker mice, pharmacology, and optogenetics to examine how the eCB system controls glutamatergic input onto NAcSh medium spiny neurons. We have found that eCB plasticity induced by low-frequency stimulation is cell-type specific. Future studies will examine how this plasticity is affected by psychostimulant exposure and abstinence with the aim of developing novel addiction therapeutics.

Disclosures: B.D. Turner: None. **E. Delpire:** None. **B. Grueter:** None.

Poster

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Support: NIDA RO1-DA033342 (AR)

NIDAvP50-DA015369 (PI: AR, PD: P. Kalivas)

Title: Cocaine and Stress disrupt mGluR/SK inhibition on dopamine neurons of the VTA

Authors: *J. PARRILLA-CARRERO, E. POTAPENKO, A. RIEGEL;
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Abstract: Both environmental stressors and drugs of abuse cause enduring cellular adaptations in the ventral tegmental area (VTA) which contribute to addiction. In rats with a history of cocaine use, stressors promote relapse of drug seeking by enhancing corticotrophin-releasing factor (CRF) signaling in the VTA. One potential mechanism by which stress and drugs of abuse overlap is the induction of CRF-dependent plasticity at glutamatergic synapses. The interaction between stress, drugs of abuse, CRF, and glutamate in the VTA, however, remains poorly understood. Aside from promoting excitatory signaling via ionotropic receptors, glutamate also recruits inhibition in VTA neurons via the activation of postsynaptic metabotropic glutamate receptors (mGluRs), mGluRs mobilize intracellular calcium stores to activate inhibitory sK channels. This Ca2+-dependent signaling is potentiated by CRF. Here, using whole cell patch

clamp electrophysiology recordings from VTA neurons, we investigated mGluR - sK channel inhibition after single and repeated exposure to the ecologically valid stressor TMT (a component of fox odor), or repeated exposure to cocaine. Single TMT exposure facilitated mGluR - SK currents, an adaption normalized by either the CRF receptor 1 (CRF-R1) antagonist CP-156254 or the CRF receptor 2 (CRF-R2) antagonist K41498. However, repeated TMT exposure weakened the evoked mGluR - SK current, a condition that was unabated by blockade of CRF-R2. In addition, repeated TMT exposure significantly increased the frequency of spontaneous miniature outward currents (SMOCs). These SMOCs were observed prior to synaptic stimulation, persisted in the presences of TTX, and were blocked by either depletion of intracellular calcium stores with CPA, or by the irreversible sK channel blocker apamin. Activation of sK channels may be enhance due to dysregulated calcium leak from intracellular stores. Interestingly, repeated administration of cocaine (IP) with 7-14 days of withdrawal resulted in similar increases in SMOCs. We propose that cocaine as well as stress, alters mGluR inhibition in DA neurons through impairment of intracellular Ca2+ signaling.

Disclosures: J. Parrilla-Carrero: None. **E. Potapenko:** None. **A. Riegel:** None.

Poster

778. Cocaine: Cellular and Synaptic Studies

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Topic: C.17. Drugs of Abuse and Addiction

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Title: Cocaine mediated molecular regulation of mitochondrial dynamics in nucleus accumbens projection neuron subtypes

Authors: *R. CHANDRA[1], C. FRANCIS[1], M. ENGELN[1], A. AMGALAN[1], L. JENSEN[1], P. KONKALMATT[2], A. GANCARZ[3], S. GOLDEN[4], D. DIETZ[3], G. TURECKI[5], S. RUSSO[4], M. LOBO[1];
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Abstract: Altered brain energy homeostasis is a hallmark adaptation occurring in the cocaine-addicted brain. This includes alterations in glucose metabolism, glutamate homeostasis, and oxidative stress. Recent studies demonstrate that mitochondria dysfunction is associated with psychiatric disorders. However, mitochondrial dynamics have not been thoroughly addressed in cocaine abuse. Our data demonstrate that genes important for mitochondria biogenesis and function are upregulated in nucleus accumbens (NAc) of rodents that self-administer cocaine (FR1 schedule, 1mg/kg/infusion) and in postmortem NAc of cocaine dependent individuals. We next examined mitochondrial biogenesis and function genes in the two NAc projection medium spiny neuron (MSN) subtypes, those enriched in dopamine D1 vs. D2 receptors. Using the RiboTag methodology, we observe an up-regulation of ribosome-associated mRNA of many mitochondrial biogenesis and function genes in D1-MSNs but a decrease in D2-MSNs after repeated cocaine (7 days, 20 mg/kg). We have generated a Cre inducible adeno-associated virus (AAV)-double inverted floxed open reading frame (DIO)-mito-dsRed to label mitochondria in D1-MSNs and D2-MSNs using D1-Cre and D2-Cre mouse lines. This will allow us to examine mitochondrial volume and number in MSN subtypes after repeated cocaine exposure. Additionally, we have developed an AAV-DIO to overexpress peroxisome proliferator-activated receptor-gamma coactivator-1α (Pgc1α), a transcriptional coactivator of mitochondrial biogenesis and function genes. Overexpression of Pgc1α in NAc D1-MSNs enhanced cocaine conditioned place preference and cocaine-induced locomotion, while Pgc1α expression in D2-MSNs reduced these behaviors. Another gene we are pursuing is dynamin-related protein 1 (Drp1), a GTPase that directly binds to the outer mitochondrial membrane to promote mitochondria division hence it plays an important role in generating new mitochondria. We find that the active form of Drp1 protein is increased in NAc and the Drp1 gene is increased in D1-MSNs but reduced in D2-MSNs after repeated cocaine (7 days, 20mg/kg). We are developing Cre-inducible AAVs for wildtype, constitutively active, and a dominant-negative Drp1 so we can test Drp1 function in MSN subtypes in cocaine-related behaviors. Collectively, our findings demonstrate altered molecular mechanisms governing mitochondrial dynamics in the two MSN subtypes with cocaine exposure.

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Poster

778. Cocaine: Cellular and Synaptic Studies

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P50 - DA015369

R01 - DA033342

Title: Cocaine self-administration and cue-reinstatement disrupt Kv7 (KCNQ) channel inhibition in the prefrontal cortex

Authors: *W. BUCHTA, A. RIEGEL;
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Abstract: In human cocaine addicts, re-exposure to drug-paired cues induces hyperactivity in the prefrontal cortex (PFC) that precipitates drug-craving and relapse. While the underlying mechanisms are unknown, they likely involve cellular adaptations in intrinsic ion channel signaling. For example, pyramidal cells in the PFC normally display robust spike-frequency adaptation (accommodation) that limits repetitive neuronal firing. This firing pattern is mediated in part by Kv7 (KCNQ) K+ channels, which are activate at subthreshold potentials, are non-inactivating, and are sensitive to inhibition by multiple neuromodulators known to be released in response to cues. Therefore, using whole cell patch clamp electrophysiology we recorded from L5 pyramidal cells in the prelimbic (PL) PFC of rats after a history of chronic cocaine self-administration and extinction training, with or without re-exposure to cocaine-paired cues and investigated Kv7 channel function. After cocaine self-administration and extinction, cells demonstrated (a priori) hyperexcitable firing rates, loss of spike accommodation, and reduced Kv7 channel inhibition. These adaptations could be normalized by acute blockade of dopamine D1 receptors, inhibition of PKA, depletion of intracellular Ca2+, or stabilization of Kv7 ion channels directly with retigabine. This suggests that excessive dopamine D1 receptor signaling disrupts Kv7 channel function. Re-exposing rats to cocaine-paired cues for 30min further enhanced neuronal excitability, involving calcium-store dependent desensitization of Kv7 channel activity. These cellular adaptations may contribute to cue-induced drug seeking, since *in vivo* infusion of retigabine into the PFC prior to cue-induced reinstatement testing blocked cocaine-seeking behavior. Taken together these data suggest that chronic cocaine experience enhances cue-induced PFC excitability by disrupting intrinsic Kv7 channel mediated spike accommodation, resulting in repetitive neuronal firing in response to depolarizing (excitatory) inputs. This neuroadaptation may underlie the enhanced saliency of drug-related cues that trigger relapse in cocaine addicts.

Disclosures: W. Buchta: None. **A. Riegel:** None.

Poster

778. Cocaine: Cellular and Synaptic Studies

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Title: Dynamic changes in nucleus accumbens miR-495 expression across cocaine self-administration and reinstatement

Authors: *R. M. BASTLE[1], N. S. PENTKOWSKI[1], P. R. KUFAHL[2], N. A. PEARTREE[2], T. CHAUDHURY[1], C. D. SMITH[1], R. J. OLIVER[3], N. I. PERRONE-BIZZOZERO[3], J. L. NEISEWANDER[1];
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Abstract: We previously found that the microRNA miR-495 is highly expressed in the striatum, targets several addiction-related genes (ARGs), and is downregulated in the nucleus accumbens (NAc) 1 h following both acute and sensitizing cocaine injection regimens. We then found that miR-495 overexpression in the NAc shell (NAcSh) decreases ARG expression, cocaine self-administration (SA) under a progressive ratio schedule of reinforcement, and responding during extinction and reinstatement. These findings suggest miR-495 regulates genes that are involved in motivation for cocaine. Here, we sought to characterize changes in NAc miR-495 expression across different lengths of cocaine SA, and following cue and cocaine-primed reinstatement. Adult, male Sprague-Dawley rats were trained to lever press for cocaine (1.0 mg/kg/0.1ml, IV) under a variable ratio (VR) 5 schedule of reinforcement. Control rats received yoked saline infusions. Rats were sacrificed 1 h following either the 1st (i.e., Day 1 group) or the 22nd SA session that either followed a 1- or 21-d abstinence period (i.e., Day 22 or Relapse group, respectively). Total RNA was isolated from NAc tissue and miR-495 expression was measured using qRT-PCR. We found that miR-495 levels were significantly increased in the Day 1 and Day 22 SA groups in the NAcSh compared to saline controls, but no change was found in the NAcSh of the Relapse group or between any groups in the NAc core. A separate group of rats underwent SA training (0.75 mg/kg/0.1ml, IV; VR5), followed by daily extinction sessions, and then were either tested for cue or cocaine-primed reinstatement. For cocaine-primed

reinstatement, cocaine- and saline-trained rats received either a cocaine (15 mg/kg, IP) or saline injection on test day. Rats were sacrificed immediately following the 90-min test session. We found no change in NAc miR-495 expression following cue reinstatement, but did find a significant decrease following a cocaine-prime on test day, regardless of whether rats were trained with cocaine or saline. This latter effect is consistent with our previous findings where experimenter-delivered cocaine downregulates NAc miR-495 expression. In contrast, self-administered cocaine upregulates miR-495 levels, specifically in the NAcSh. This effect only occurs during SA acquisition and maintenance, suggesting miR-495 increases in the early stages of acquiring cocaine abuse-related behavior, but not in later stages. Given that miR-495 targets several ARGs and increasing its expression in the NAcSh suppresses motivation for cocaine, the blunted increase in miR-495 during relapse may contribute to neuroadaptations underlying cocaine dependence.

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Poster

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Title: The neuronal RNA-binding protein HuD interacts with Argonaute proteins and GW182 proteins in an RNA-dependent manner relieving miRNA-mediated repression

Authors: A. S. GARDINER, M. DELL'ORCO, *N. PERRONE-BIZZOZERO; Neurosciences, Univ. of New Mexico HSC, Albuquerque, NM

Abstract: The RNA stability factor HuD is an RNA-binding protein that binds specific U-rich sequences in the 3'UTR of target mRNAs. This interaction serves to stabilize mRNAs, allowing for increased translation of the targets. MicroRNAs (miRNAs) also bind specific sequences in the 3'UTR of target mRNAs, but unlike HuD, this interaction most often results in decreased translation through silencing or degradation. MiRNAs function in the context of the RNA-

induced silencing complex (RISC), which includes Argonaute (Ago) proteins. Ago proteins interact with GW182 proteins, which are required for miRNA-mediated gene silencing. GW182 proteins accumulate in GW-bodies, also known as P-bodies, which are sites for mRNA degradation. mRNAs may also be stored in P-bodies, in the cell body as well as in neuronal processes, until they are needed. Previously, we reported that HuD and miR-495 have many target mRNAs in common, as the miR-495 seed sequence is complementary to the HuD GU-rich binding motif and that many of these common targets are implicated in drug addiction (Gardiner et al. 2013; SfN Poster 350.10). Thus, HuD and miR-495 compete for the binding and regulation of addiction-related genes such as BDNF and CAMK2a, which are enriched in shared binding-sites in their 3'UTRs. Interestingly, when HuD was transfected into HeLa cells that were previously subjected to miR-495-mediated repression, reporter constructs showed robust derepression. However, the opposite did not occur when miR-495 was added to cells previously treated with HuD. Here we show that in the mouse striatum, a region important for addiction-related processes, HuD interacts with Ago proteins and that this interaction is in part RNA-mediated. We also show that HuD interacts with the P-body marker GW182. In addition, HuD colocalizes with GW182 in neuroblastoma cells treated with hydrogen peroxide. These findings suggest a mechanism by which HuD may "rescue" mRNAs from miRNA-mediated repression in P-bodies, allowing for increased translation. Furthermore, since HuD is expressed in the nucleus accumbens and regulated by cocaine, HuD-mediated target derepression may be involved in the post-transcriptional control of gene expression during the establishment of addiction-related behaviors.

Disclosures: **A.S. Gardiner:** None. **M. Dell'Orco:** None. **N. Perrone-Bizzozero:** None.

Poster

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Topic: C.17. Drugs of Abuse and Addiction

Support: 1R01DA034097

Title: Neuronal rna-binding protein hud regulates addiction-related target mrnas, structural plasticity, and cocaine addiction-related behaviors

Authors: ***R. J. OLIVER, JR**, A. S. GARDINER, J. L. BRIGMAN, A. M. ALLAN, N. I. PERRONE-BIZZOZERO;
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Abstract: Post-transcriptional mechanisms play an important role in nervous system development and function, however, very little is known about their role in the etiology of substance use disorders. RNA binding proteins (RBPs) provide one such regulatory mechanism in post-transcriptional regulation. HuD is a neuronal specific RBP that associates with the 3'UTR of specific mRNAs containing AU-rich instability elements (AREs). Through association with these regions, HuD stabilizes mRNA transcripts protecting them from degradation. We found that HuD targets include those that have been implicated in addiction, including CaMKIIa, Bdnf, Mef2c, and Arc. Additionally, HuD (ELAVL4) itself was found within the KARG suggesting it may play a role in this disorder. Using a dual luciferase expression system, we demonstrated that the Camk2a, Arc, and the long and short 3' UTR variants of BDNF transcripts (Bdnf-L, Bdnf-S) are direct targets of HuD. Confirming this, we found that mice overexpressing neuronal specific HuD (HuD OE; Camk2a-myc-ELAVL4/Npb; Bolognani et al., 2006) had increased mRNA expression of targets such as CaMKIIα and Bdnf, especially within the Nucleus Accumbens (NAc). Increased protein expression of these targets was also found within this region. Since many HuD targets have roles in structural plasticity of neurons, specifically within the NAc, we were interested in the role that HuD may play in this phenomenon. We found that HuD OE animals had increased percentage of immature thin spines, with a decrease in intermediate stubby spines within NAc neurons. However, there were no differences in the percentage of mature mushroom spines. Next, we were interested in the translation of these molecular and structural alterations to behavior. We found that HuD OE mice are more sensitive to the acute locomotor stimulatory actions of 7.5 mg/kg cocaine compared to wild type (WT) littermates. Although their initial response to cocaine was elevated, the animals did not exhibit sensitization to cocaine suggesting a ceiling effect of drug-induced locomotor activity. In a conditioned place preference model, we found that HuD OE spend more time in the cocaine (15 mg/kg) associated chamber compared to WT littermates. Finally, this effect may be limited to drug associated cues, as HuD OE and WT animals did not show a difference in their acquisition or extinction of appetitive behavior. However, upon exposure food-paired cues, HuD OE animals show increased reinstatement behavior. Together, these results suggest that HuD may play a role in addiction-related alterations in gene expression, plasticity, and behavior.

Disclosures: R.J. Oliver: None. **A.S. Gardiner:** None. **J.L. Brigman:** None. **A.M. Allan:** None. **N.I. Perrone-Bizzozero:** None.

Poster

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Topic: C.17. Drugs of Abuse and Addiction

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Title: Cadherin adhesion complexes and cocaine-mediated synaptic plasticity

Authors: *A. K. GLOBA[1], F. MILLS[1], S. LIU[3], C. M. COWAN[1], S. L. BORGLAND[3], A. G. PHILLIPS[2], S. X. BAMJI[1];
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Abstract: Variations in cadherin-catenin adhesion complex genes are associated with multivariate drug use, however the role of these proteins in drug-mediated synaptic plasticity has not been defined. Here we demonstrate that classical cadherins N-cadherin, R-cadherin, and cadherins -7, -8, and -11 are expressed in dopaminergic (DA) and non-dopaminergic neurons of the VTA and that N-cadherin is localized to both excitatory and inhibitory synapses being formed onto these DA neurons. Inhibiting intercellular N-cadherin interactions abolished spike-timing dependent plasticity in the VTA, indicating that cadherins are important mediators of synapse plasticity in this region. Using immuno electron microscopy we demonstrate that following cocaine-mediated conditioned place preference (CPP), cadherin and GluA1 are significantly recruited to the synaptic membrane of excitatory synapses being formed onto dopaminergic neurons. This is reversed following extinction of CPP. Moreover, stabilizing cadherin at the membrane using a transgenic mouse model significantly attenuates cocaine-mediated CPP. These results show that cadherins play an important role in synaptic plasticity in the VTA and may be involved in structural changes at synapses caused by cocaine use.

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Poster

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Title: Phasic neuronal activity in the anterior cingulate cortex robustly differentiates water and cocaine cues in rhesus macaque monkeys

Authors: J. T. MORRA[1], E. BAEG[2], H. P. JEDEMA[3], *C. W. BRADBERRY[3,4];
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Abstract: Prior studies in rodents suggest that cues associated with natural rewards, such as food and water, are represented by phasic activity in a common, overlapping subpopulation of neurons in the ventral striatum. Conversely, phasic cocaine cue encoding has been shown to manifest in a parallel, largely non-overlapping ensemble of neurons in that region. Though these electrophysiological studies have substantiated parallel processing of motivationally salient cues in the rodent ventral striatum, the topography of encoding of drug vs non-drug reward is less well characterized in the primate brain. Rodent functional imaging data implicate a broad tapestry of brain reward circuitry in the differentiation of cocaine and natural reward cues, including the dorsal striatum and medial prefrontal cortex. In primates, both orbitofrontal and anterior cingulate cortex have been shown to selectively encode distinct non-drug rewards. The purpose of the current study was to extend electrophysiological differentiation of cocaine versus non-drug reward associated cues to a broader neuroanatomical framework in the non-human primate brain. We simultaneously recorded multiple single units in the ventral and dorsal striatum, as well as the anterior cingulate and orbitofrontal cortices of rhesus monkeys during both water and cocaine self-administration blocks within the same sessions. We identified differential encoding of water and cocaine cues across all brain regions. However, we found that neurons in the anterior cingulate cortex distinguish cocaine from water cue conditions more robustly than neurons in the other regions of interest. These data implicate the anterior cingulate cortex as a structure of particular importance in the differentiation of drug and non-drug reward.

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Poster

778. Cocaine: Cellular and Synaptic Studies

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 778.17/I21

Topic: C.17. Drugs of Abuse and Addiction

Title: Cocaine evokes microvesicle release by activating sigma-1 receptor and ARF6

Authors: *Y. NAKAMURA[1], S.-Y. TSAI[1], Y. LI[2], D.-T. LIN[2], T.-P. SU[1];
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Abstract: The sigma-1 receptor (Sig-1R) is known to function as a chaperone and has been implicated in many central nerve system disorders including depression, neuropathic pain and drug addiction. We reported previously that the Sig-1R can translocate (e.g., from mitochondrion-associated endoplasmic reticulum membrane to the endoplasmic reticulum network and plasma membrane) after the agonist stimulation and shapes therefore neuronal and behavioral responses to cocaine which is a Sig-1R agonist (Kourrich et al., Cell, 2013). Given that a recent clinical study demonstrated that Sig-1Rs are present in the plasma and that the concentration of Sig-1Rs increased following the treatment of antidepressants including fluvoxamine which is a Sig-1R agonist (Shimizu H et al., Neuropsychiatr Dis Treat. 2013), we previously examined the possibility that cocaine may cause Sig-1Rs to translocate into extracellular space in the form of extracellular vesicles that may represent a new route of shaping neuroplasticity induced by cocaine. Thus, our previous study showed that Sig-1Rs were found in the isolated microvesicles following a 30 min treatment of cocaine and that the extracellular Sig-1R level increased in a cocaine dose-dependent manner (0.1, 1 and 10 μM). Furthermore, pre-treatment with BD1063, a specific Sig-1R antagonist, completely inhibited the cocaine-evoked release of microvesicles containing Sig-1R (Nakamura et al., SfN 2014). However, the mechanisms underlying cocaine-induced microvesicle release are still unknown. The present study examined the effect of cocaine on the activity of ADP-ribosylation factor 6 (ARF6) which is a small GTP-binding proteins and is known to be an important signaling molecule to regulate microvesicle release and membrane trafficking. Indeed, cocaine stimulation increased an active form of ARF6 (ARF6-GTP). Those results indicate that the activation of Sig-1R by cocaine in causing microvesicle release may involve ARF6. (supported by IRP NIDA NIH)

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Poster

778. Cocaine: Cellular and Synaptic Studies

Location: Hall A

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Topic: C.17. Drugs of Abuse and Addiction

Support: 'Plan Nacional sobre Drogas' (MSSSI, Spain): Grant 2012I011 (to MJGF)

Fundación Alicia Koplowitz (to MJGF)

RTA-RETICS: RD12/0028/0011 (MINECO, Spain)

MJGF is a 'Ramon y Cajal' Researcher (MINECO, Spain)

Title: Opposite regulation of cannabinoid CB1 and CB2 receptors in the prefrontal cortex of rats treated with cocaine during early adolescence

Authors: *J. GARCIA-FUSTER, R. GARCIA-CABRERIZO;
IUNICS. Univ. of the Balearic Islands, Palma de Mallorca, Spain

Abstract: The endocannabionoids function as retrograde lipid messengers through the activation of inhibitory CB1 and CB2 receptors. CB1 is highly expressed in the cerebral cortex and other limbic areas of the brain reward circuitry, while CB2 is less abundant and is mainly associated with inflammatory processes mediated by microglia. The endocannabinoid system is implicated in the neurobiology of cocaine addiction, even though the literature shows inconsistent findings in how chronic cocaine regulates CB1 and CB2 receptors in the brain. Given that adolescence represents a critical moment for shaping adult behavior and may predispose to disease vulnerability later in life, this study evaluated: (1) the basal regulation of cannabinoid CB1 and CB2 receptors in several brain regions (i.e., prefrontal cortex, PFC and hippocampus, HC) during the course of adolescence (post-natal day PND 40, PND 47, PND 54) as compared to adulthood (PND 61), and (2) the regulation of brain CB1 and CB2 receptors by a sensitizing regimen of chronic cocaine (15 mg/kg, 7 d, i.p.) during different windows of adolescence vulnerability (early PND 33-39, mid PND 40-46, late PND 47-53). Control rats received 7 consecutive days of saline (0.9% NaCl, i.p., 1 ml/kg) at the indicated windows of adolescence. CB1 and CB2 receptor protein levels were evaluated in the PFC and HC by western blot analysis with specific and validated antibodies 24 h after the last treatment dose (PND 40, PND 47, PND 54). The results demonstrated a dynamic and opposite basal modulation of CB1 and CB2 receptors during the course of adolescence. In particular, CB1 receptor levels were increased while CB2 receptors were decreased in adolescence as compared to adulthood with asymptotes values around mid adolescence (PND 47) both in PFC (CB1: +45±22, $p<0.05$; CB2: -24±6%, $p<0.05$) and HC (CB1: +53±23, $p<0.05$; CB2: -20±8%, $p<0.05$). Interestingly, chronic cocaine only regulated CB1 (+55±10%, $p<0.05$) and CB2 (-25±10%, $p<0.05$) receptors when it was administered during early adolescence and only in the PFC. These results identified a period of vulnerability during early adolescence at which cocaine dysregulated the activation of CB receptors in the PFC. Further studies are evaluating whether these changes are transient or can interfere in the normal program of brain development and have enduring consequences beyond that age period and into adulthood.

Disclosures: J. Garcia-Fuster: None. **R. Garcia-Cabrerizo:** None.

Poster

778. Cocaine: Cellular and Synaptic Studies

Location: Hall A

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Program#/Poster#: 778.19/I23

Topic: C.17. Drugs of Abuse and Addiction

Support: NARSAD

Marie Curie CIG

Title: Role of hevin in the neuroplasticity of cocaine addiction

Authors: *V. F. VIALOU, R. MONGRÉDIEN, A. ORRICO, A. ERDOZAIN;
INSERM, Paris, France

Abstract: Exposure to addictive drugs can result in maladaptive alterations in neural circuit function, which underlie the addicted phenotype. While alteration in synaptic plasticity in corticoaccumbens circuit has long been caracterized as a core factor in addiction, extracellular matrix proteolysis has recently been implicated in mediating addiction. The focus of my research is on a matricellular protein called Hevin that is expressed in the nucleus accumbens and has been shown to play a role during development on synpatogenesis. We first performed double fluorescent *in situ* hybridization to characterize hevin expression in nucleus accumbens in the adult mouse brain. We could confirm hevin expression in specific cell types: neurons and astrocytes. We then quantified hevin protein levels in the nucleus accumbens after acute or chronic cocaine administration. Hevin was upregulated only by chronic cocaine. In order to evaluate its orle in sensitivity to cocaine, we used viral-mediated gene transfer into nucleus accumbens to overexpress hevin. We also used the complementary approach to downregulate hevin expression via the expression of shRNA directed against hevin. Finally, we used hevin knock-out mice. After hevin manipulation, we subjected the mice to conditioned place-preference. We show here that viral overexpression of hevin in the entire NAc decreases cocaine's rewarding effect. Surprisingly, downregulation or lack of hevin also decreases cocaine's rewarding effect. This points to a complex role of hevin in the neuronal plasticity associated to the adaptation to drugs of abuse. Alterations in spine morphology and numbers are key features of chronic exposure to cocaine and might mediate the cognitive impairments and mood disturbances of various diseases. My preliminary studies show that hevin in NAc basally increased spine density and this effect was potentiated after repeated cocaine. This is in accordance with its synaptogenic role at excitatory synapse in neuronal cultures and *in vivo* in optic tectum. We are currently testing the effects of hevin upregulation in specific neuronal subtypes. Long-term alterations in the nucleus accumbens contribute to the behavioral abnormalities observed after cocaine administration. We identified hevin as a key player of

cocaine's rewarding effects. Alteration in hevin's level alter cocaine sensitivity but increases spine number. Together these experiments will provide better understanding of the role of hevin in the pathophysiology of drug addiction.

Disclosures: V.F. Vialou: None. **R. Mongrédien:** None. **A. Orrico:** None. **A. Erdozain:** None.

Poster

778. Cocaine: Cellular and Synaptic Studies

Location: Hall A

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Program#/Poster#: 778.20/I24

Topic: C.17. Drugs of Abuse and Addiction

Support: NIH Grant DA033404

Title: Enhanced sensitivity to repeated cocaine increases perineuronal net staining in the adult rat medial prefrontal cortex

Authors: *M. SLAKER, B. A. SORG;
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Abstract: Perineuronal nets (PNNs) are unique structures of extracellular matrix in the central nervous system. Within the medial prefrontal cortex, PNNs surround the soma and proximal dendrites of parvalbumin (PV)-containing, GABAergic interneurons. The appearance of PNNs during development coincides with the closure of critical periods, during which time external stimuli influence development of neuronal circuits. Cocaine is a psychomotor stimulant that increases locomotor activity in rats; after repeated cocaine exposure, rats become sensitized to cocaine and display an enhanced locomotor response. We sought to determine the effect of cocaine exposure on PNNs within the medial prefrontal cortex. We hypothesized that exposure to a strong external stimulus (cocaine) during adulthood would increase the intensity of PNNs within the prefrontal cortex. To test this, we exposed adult, male rats to 1 or 5 days of cocaine (15 mg/kg, i.p.) and locomotor activity was measured each day to assess sensitization. Two hours following the last injection, rats were sacrificed and the prefrontal cortex was assessed for PNN intensity. Preliminary results suggest that 2 hr following the last cocaine injection, PNN intensity was increased in the prelimbic region of the prefrontal cortex but was unaffected in the infralimbic or medial orbitofrontal regions. This increased intensity was positively correlated with sensitized locomotor activity, suggesting that PNN intensity in the prelimbic region may serve as a functional read-out of cocaine-induced motivational behavior. In addition to PNNs, we

also analyzed PV expression. These results demonstrate that exposure to cocaine increases PNN intensity within the prelimbic region of the prefrontal cortex and suggest that repeated cocaine may render the medial prefrontal cortex resistant to normal physiological stimuli.

Disclosures: M. Slaker: None. **B.A. Sorg:** None.

Poster

778. Cocaine: Cellular and Synaptic Studies

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Topic: C.17. Drugs of Abuse and Addiction

Support: DA009621

DA036327

Title: Emergence of endocytosis-dependent mglur1-ltd at nucleus accumbens synapses during withdrawal from cocaine self-administration

Authors: *A. F. SCHEYER[1], M. E. WOLF[2], K. Y. TSENG[3];
[1]Neurosci., Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL; [2]Neurosci., [3]Cell. and Mol. Pharmacol., Rosalind Franklin Univ., North Chicago, IL

Abstract: Extended-access cocaine self-administration induces a progressive enhancement of cocaine craving during withdrawal termed “incubation of craving”. Rats evaluated after >1 month of withdrawal (“incubated rats”) display alterations in signaling at medium spiny neuron (MSN) synapses of the nucleus accumbens (NAc), including elevated levels of Ca2+-permeable AMPA receptors (CP-AMPARS) and a transition in group I metabotropic glutamate receptor (mGluR)-mediated synaptic depression from mGluR5- to mGluR1-dependent. To determine the time-course over which these adaptations appear and further characterize the emergent form of mGluR1-mediated synaptic depression, we conducted whole-cell patch-clamp recordings in NAc core MSN of “incubated rats” at multiple time-points during withdrawal. Elevated synaptic contributions from CP-AMPARs, as well as the loss of mGluR5- and gain of mGluR1-mediated synaptic depression, were not detected between 7 and 25 days of withdrawal, but were present following at least 35 days. Furthermore, the previously identified mGluR1-mediated suppression of the EPSC was found to be a form of long-term depression (mGluR1-LTD). We also investigated the mechanism underlying this mGluR1-LTD by conducting recordings in the presence of dynamin inhibitory peptide or pep2-EVKI, which disrupt endocytosis and PICK1

regulation of calcium-impermeable AMPAR (CI-AMPAR) trafficking, respectively. Together, our results indicate that mGluR1-LTD involves a non-obligatory swap of CP-AMPARs and CI-AMPARs mediated by dynamin-dependent internalization and PICK1-dependent insertion. Together, these results elucidate the time-course for the emergence of multiple adaptations during withdrawal, in addition to the mechanisms underlying mGluR1-LTD at NAc MSN synapses after the "incubation" of cocaine-craving.

Disclosures: A.F. Scheyer: None. **M.E. Wolf:** None. **K.Y. Tseng:** None.

Poster

779. Amphetamines: Mechanisms of Addiction and Sensitization

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Support: R21DA033182

P50DA018165-04P1

P50DA018165

2010-DD-BX-0575

This material is the result of work supported with resources and the use of facilities at the VA Portland HCS.

Title: Effect of naltrexone on neural response to risky decision making

Authors: P. T. KORTHUIS[1], L. DENNIS[1], R. LISOWSKI[1], D. SCHWARTZ[1], B. TREMBLAY[1], V. WILSON[1], *W. F. HOFFMAN[2,1];
[1]Oregon Hlth. & Sci. Univ., Portland, OR; [2]Mental Hlth. Div. P35C, Portland VA Med. Ctr., Portland, OR

Abstract: Introduction: Persons who use methamphetamines (MA) often engage in risky decision-making. Naltrexone blocks opioid mu receptors in the reward pathway that may modulate impulsivity. We assessed the effect of naltrexone on impulsivity and its neural correlates in MA dependence. **Methods:** We evaluated 42 MA-dependent participants on a probability-delay discounting (PDD) fMRI task before and 3 weeks after randomization to extended-release naltrexone (XR-NTX 380mg) or placebo injection. The PDD asks participants

to choose between an immediate, certain monetary reward and alternative reward of varying magnitude, time to receipt, and odds against winning. We calculated area under the curve (AUC) for delay and probability. AFNI amplitude modulated regression identified brain regions whose BOLD response scaled with the size of the reward characteristic. Linear mixed models assessed within subject (time) by group main effects and interaction (voxel threshold p=0.01; cluster threshold familywise $\alpha<0.05$). **Results:** Participants were similar by treatment group (Table). Performance on the PDD did not differ between groups over time, but probability AUC decreased for XR-NTX group, suggesting decreased impulsivity. fMRI analysis found significant treatment by time interaction clusters for probability and delay (Figure). Cluster voxels were less responsive to stimulus in the NTX group, but unchanged for placebo.

Table: Comparison of demographic and discounting measures between groups before and after XR-NTX injection.

	Demographics			PDD			
				Delay		Probability*	
	Age (SD)	% Male	Education (SD)	pre	post	pre	post
XR-NTX (19)	39.3 ± 10.6	76.0	12.6 ± 2.04	0.61 ± 0.25	0.61 ± 0.24	0.36 ± 0.25	0.31 ± 0.26
Placebo (23)	36.7 ± 9.53	70.4	12.5 ± 0.77	0.47 ± 0.24	0.50 ± 0.21	0.34 ± 0.19	0.26 ± 0.12

*Significant main effect of visit ($F(1,40) = 5.7$, $p = 0.021$).

Conclusions: In this sample, XR-NTX decreased sensitivity to delay and probability in behaviorally relevant brain regions. The PDD may be useful for studying the neural basis of behavioral response to other substance use disorder treatments.

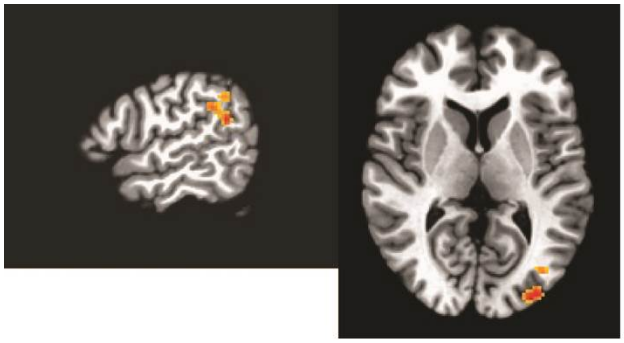

Figure: Regions with significant group x time interaction terms. Left, right inferior parietal lobule for the AM regressor associated with probability; right, occipito-parietal junction for the AM regressor associated with delay.

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Poster

779. Amphetamines: Mechanisms of Addiction and Sensitization

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Topic: C.17. Drugs of Abuse and Addiction

Support: Grant from NECSA (Nuclear Energy Corporation of South Africa)

Title: Imaging of cerebral glucose metabolism in methamphetamine dependence with and without psychosis compared to normal controls: a PET study

Authors: D. VULETIC[1], J. WARWICK[2], T. MOALOSI[2], J. ZEEVAART[3], *P. DUPONT[4], D. STEIN[1];
[1]Dept. of Psychiatry, Univ. of Cape Town, Cape Town, South Africa; [2]Dept. of Nuclear Med., Stellenbosch Univ., Cape Town, South Africa; [3]Nuclear Energy Corp. of South Africa (NECSA), Johannesburg, South Africa; [4]Lab. for Cognitive Neurol., KU LEUVEN, Leuven, Belgium

Abstract: Objective: Methamphetamine dependence may lead to a range of psychiatric and medical symptoms, including psychotic symptoms. However, there are few PET data that include patients with methamphetamine dependence who do and do not have psychosis. We used positron emission tomography (PET) with [18F]fluorodeoxyglucose (FDG) to investigate the neurocircuitry of methamphetamine dependence with and without psychotic symptoms. Methods: Resting brain glucose metabolism was measured with FDG-PET using a Philips Gemini PET-CT scanner in three groups: ten patients with methamphetamine dependence, twelve patients with a history of methamphetamine induced psychotic disorder (both these groups of participants were abstinent for a minimum of one week), and eleven normal controls. After normalization for whole brain counts, warping to MNI (Montreal Neurological Institute) and smoothing with a 12mm Gaussian kernel, we performed a voxel based ANOVA using SPM8. The significance threshold was set at FWE corrected $p < 0.05$. Results: In the methamphetamine dependence group with no psychosis, significantly decreased glucose metabolism was seen in the anterior right cingulum compared to the control group ($x=14, y=42, z=12$, $T=5.23$, FWE corrected $p=0.02$, cluster size=1067). No significant differences were seen between the other group comparisons. Conclusion: Lower metabolism in the cingulum in methamphetamine dependence is consistent with previous reports showing decreased activity

in this region in recently abstinent patients. Such decreased metabolism has been suggested to contribute to impaired cognitive and emotional processes in these patients. The lack of findings in those patients with a history of psychosis is contrary to expectations, and may reflect normalization by antipsychotic treatment.

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Poster

779. Amphetamines: Mechanisms of Addiction and Sensitization

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Title: Differential effects of Methamphetamine and Modafinil on the mRNA levels of dopamine and glutamate receptors and voltage-gated Ca^{2+} channels in the mouse prefrontal cortex

Authors: *V. BISAGNO[1], B. GONZALEZ[2], J. CADET[3], E. GARCIA-RILL[4], F. J. URBANO[5]; [1]ININFA-CONICET, Buenos Aires, CABA, Argentina; [2]ININFA-(UBA-CONICET), Buenos Aires, Argentina; [3]Mol. Neuropsychiatry Res. Br., NIDA-NIH, Baltimore, MD; [4]Ctr. for Translational Neurosci., UAMS, Little Rock, AR; [5]IFIBYNE (UBA-CONICET), Buenos Aires, Argentina

Abstract: Abuse of methamphetamine (METH) can induce cognitive dysfunctions in humans and animal models. On the other hand, the psychostimulant Modafinil (which shares with METH the property of being also a DAT blocker) is prescribed as a cognitive enhancer. We have previously demonstrated that Modafinil can attenuate METH-induced deficits in visual memory and improve ERK signaling in the medial prefrontal cortex (mPFC). We have also reported that METH blunted calcium currents in mPFC pyramidal neurons and decreased excitatory transmission through D1/D5 receptor mechanisms. Interestingly, SCH23390 (D1/D5 antagonist) alone was able to produce similar detrimental effects on mPFC physiology. Our studies suggest inverted-U-shaped dopamine (DA) actions in mPFC: low levels of DA are beneficial (i.e.

moderate Modafinil actions), high levels are detrimental (massive dopamine release by METH). In order to unveil other potential differences in the actions of METH and Modafnil, we evaluated mRNA expression of glutamate and DA receptors subunits and voltage-gated Ca2+ channels (Cav) induced by METH (acute and chronic, 1 mg/kg) and Modafinil (acute, 90 mg/kg) in the mouse mPFC. We found that METH and Modafinil differ in their effects on mPFC as follows: (a) for DA receptors, METH decreased Drd1 mRNA while Modafinil did not; (b) Modafinil increased the expression of Drd2, METH did not; (c) for the P/Q type Cacna1a (Cav2.1), Modafinil increased its expression while METH did not show any acute effect but produced increased expression after chronic treatment; (d) for L type Cav1.3 Cacna1d, only METH showed reduced expression. On the other hand, glutamate receptor subunits mRNA AMPA Gria1 and Gria2 were increased for both psychostimulants whereas NMDA subunit Grin1 was significantly increased after acute Modafnil but only after chronic METH treatment. Western blot analysis also revealed that both drugs decreased CaMKII phosphorylation in the mPFC. In normal physiological conditions DA levels in the mPFC need to be precisely tuned to maximize signal/noise ratios. Our results support the idea that DA tuning may involve decreasing synaptic transmission (by effects on Ca currents and glutamate transmission) in cortico-cortical and cortico-subcortical networks. These mechanisms appear to be negatively impacted by toxic psychostimulants like METH to contribute to the mPFC hypofunction observed in METH addicts. Thus, some of the beneficial effects of Modafnil might be related to differential effects on DA/glutamate in the mPFC.

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Poster

779. Amphetamines: Mechanisms of Addiction and Sensitization

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 779.04/I29

Topic: C.17. Drugs of Abuse and Addiction

Title: Simultaneous determination of the effects of methamphetamine on GABA, glutamate and monoamines by microdialysis in the prefrontal cortex and hippocampus of rats

Authors: *S. C. CHEETHAM, H. ROWLEY, L. PINDER, R. KULKARNI, D. HEAL; RenaSci Ltd, Nottingham, United Kingdom

Abstract: Methamphetamine is a highly abused drug with complex pharmacological actions in the brain. Intracerebral microdialysis in freely-moving rats can provide valuable insights in such

cases, but it is often limited by the number of neurotransmitters that can be measured in each sample. We have used *in vivo* microdialysis to investigate methamphetamine's effects simultaneously on GABA, glutamate (GLU), dopamine (DA), noradrenaline (NA) and 5 HT in the prefrontal cortex (PFC) and hippocampus (HIP). Under gaseous anaesthesia, 4.0 mm microdialysis probes were stereotaxically implanted into the PFC (coordinates relative to bregma: AP +3.4 mm; ML +/-0.8 mm; DV 5.0 mm relative to dura) and HIP (AP -5.3 mm; ML +/-4.8 mm; DV -7.5 mm) of male, Wistar rats (250-350g; n=5). Dialysate samples were collected at 15 min intervals for 2 hr. GABA and GLU were analysed by UHPLC with electrochemical detection (ECD) and DA, NA, 5 HT by HPLC ECD using Antec ALEXYS™ systems. Methamphetamine (3.0 mg/kg) was dosed by intraperitoneal injection. Mean basal (T=0 min) extracellular concentrations of neurotransmitters (monoamines in fmol/5µl; amino acids in amol/1.5µl) were: PFC: DA = 3.47 ± 1.00, NA = 4.99 ± 1.98, 5 HT = 0.48 ± 0.07, GABA = 3.6 ± 2.0 and GLU = 496 ± 83; HIP: DA = 1.07 ± 0.12, NA = 3.82 ± 0.92, 5 HT = 0.12 ± 0.02, GABA = 2.4 ± 0.7 and GLU = 354 ± 27. Compared with pre-intervention baseline values, methamphetamine (3.0 mg/kg) produced rapid neurotransmitter changes that peaked 30-45min after dosing. In PFC, there were increases in DA (533%, $p<0.001$), NA (408%, $p<0.001$), 5 HT (1500%, $p<0.001$), GABA (452%, $p<0.05$) and a decrease in GLU (-56%, $p<0.001$). In HIP the same pattern of effects was observed, but the changes in monoamines were much greater with increases in DA (1781%, $p<0.001$), NA (765%, $p<0.001$), 5 HT (11,058%, $p<0.001$), GABA (451%, $p<0.01$) and a decrease in GLU (31%, $p<0.01$). The results reveal that methamphetamine produced large increases in DA and NA in PFC and HIP, but surprisingly its greatest effect was to potentiate 5 HT efflux in these regions. The increases in extracellular monoamines were accompanied by concomitant reductions in GLU and increases in GABA in both regions. It is most likely that that the decreased excitatory and enhanced inhibitory amino acid neurotransmitter efflux in PFC and HIP were homeostatic responses to attenuate the pharmacological effects of methamphetamine. The marked increases of 5 HT in both brain regions may also have been part of this response.

Disclosures: **S.C. Cheetham:** None. **H. Rowley:** None. **L. Pinder:** None. **R. Kulkarni:** None. **D. Heal:** None.

Poster

779. Amphetamines: Mechanisms of Addiction and Sensitization

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIH DA033049

DA728823

Title: Changes in cortico-striatal neuroplasticity following methamphetamine

Authors: *D. MISHRA, J. PENA BRAVO, S. M. GHEE, C. R. BERINI, A. LAVIN, C. M. REICHEL;
Dept. of Neurosciences Res., Med. Univ. of South Carolina, Charleston, SC

Abstract: Methamphetamine (meth) abuse induces changes in the prefrontal cortex (PFC) and nucleus accumbens (NAc), which exert inhibitory control over maladaptive behaviors like drug over-consumption and mediates reward-related behaviors, respectively. Hence, meth-induced functional impairment of these two regions may increase abuse vulnerability. Here, we describe changes in cortico-striatal neuroplasticity following a contingent and non-contingent meth administration protocol. In Experiment 1, rats were given 4 non-contingent i.p. injections of 4 mg/kg meth or saline at 2 hr intervals in one day. Rats were killed 7 days later and whole-cell patch clamp recordings were performed in the dorsomedial PFC (dmPFC) and field potentials in the NAc core (NAcc) of the same animals. In the dmPFC, meth increased the AMPA/NMDA ratio in meth groups compared to controls indicating potentiated state of deep-layer PFC pyramidal neurons. In the NAcc we observed a significant paired pulse depression (indicating a higher neurotransmitter release probability) in meth group when compared to controls. Also, input/output curves revealed an overall decrease in synaptic strength of meth rats. In Experiment 2, rats received one-hour meth self-administration (SA) sessions for 7 days, followed by 14 days of six-hour long access sessions and yoked saline controls. Meth was delivered IV on an FR1 schedule at a volume of 20 μg/50 μl infusion and rats were killed 7 days after discontinuation of meth. In the dmPFC, AMPA/NMDA ratio was unaffected in meth SA rats when compared to controls although, only n=2 rats have been recorded so far. In the NAcc, we assessed long term depression (LTD) and potentiation (LTP) to understand the synaptic strength using low frequency (5Hz, 900 times) and high frequency (100Hz, 4 times) stimulation protocols. Meth SA caused a loss of LTP and significantly lessened the degree of LTD induction compared to the controls. Combined, our findings indicate changes in synaptic neurotransmission in both the dmPFC and NAcc following contingent and non-contingent meth. The relationship between meth pharmacology alone or combined with behavior output has yet to be defined. Additional questions need to determine how these maladaptive consequences impact glutamate release, reuptake, and relapse to meth-seeking behavior.

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Poster

779. Amphetamines: Mechanisms of Addiction and Sensitization

Location: Hall A

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Program#/Poster#: 779.06/I31

Topic: C.17. Drugs of Abuse and Addiction

Title: Chronic methamphetamine exposure decreases neural activation in hypothalamic-pituitary-adrenal axis associated brain regions in a sex-specific manner

Authors: J. JACOBSKIND, *D. G. ZULOAGA;
Univ. at Albany, Albany, NY

Abstract: Sex differences in the abuse and consequences of methamphetamine (MA) have been reported in both humans and rodents, with females showing a more rapid spiral into addiction. One mechanism through which MA may contribute to these sex differences is by differentially activating the hypothalamic-pituitary-adrenal (HPA) axis. Our previous studies indicate that females show elevated MA-induced glucocorticoid release and altered activation of HPA axis associated brain regions following an acute exposure. However, little is known about potential sex specific effects of chronic MA on activation of HPA axis associated brain regions. In this study we administered MA (5 mg/kg) or saline to C57BL/6J mice for 10 consecutive days. Ten days after the chronic treatment period, mice were injected with a final dose of MA (5 mg/kg) or saline. Two hours later brain tissue was collected and immunohistochemically labeled for detection of the immediate early gene c-Fos in HPA-axis associated brain regions (paraventricular nucleus of the hypothalamus (PVH), central amygdala (CeA), basolateral amygdala (BLA), lateral amygdala (LA), bed nucleus of the stria terminalis (BNST), and medial amygdala (MeA)). Final injection with MA increased the number of c-Fos positive cells in all investigated regions, except the MeA. Chronic exposure to MA reduced c-Fos in the PVH, BNST, CeA, and the BLA and in three of these areas (BNST, CeA, and LA) this reduction was greater in males. In the PVH, final injection with MA increased c-Fos to a greater extent in females compared to males regardless of whether they had previously been exposed to MA. Together our findings demonstrate that chronic MA can suppress subsequent activation of HPA axis associated brain regions and in select regions this suppression is sex specific. In turn, these changes may contribute to sex differences in MA abuse patterns reported in humans and rodents.

Disclosures: J. Jacobskind: None. **D.G. Zuloaga:** None.

Poster

779. Amphetamines: Mechanisms of Addiction and Sensitization

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 779.07/I32

Topic: C.17. Drugs of Abuse and Addiction

Title: Microinjection of CART Peptide 55-102 into the nucleus accumbens blocks amphetamine-induced locomotor activity by regulating Akt-GSK3β signaling pathway

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Abstract: It has been previously shown that psychostimulants-induced locomotor activity are significantly attenuated by microinjections of cocaine- and amphetamine- regulated transcript (CART) 55-102 peptide into the nucleus accumbens (NAcc), suggesting that CART peptides exert an antagonistic effect on the generation of locomotion by these drugs in this site. In order to further identify what signal pathway might be involved in this process, we examined, in the present study, the effect of CART 55-102 on amphetamine (AMPH)-induced decreases of GSK3β and Akt phosphorylation levels in the NAcc tissues obtained from the rats which were given systemic injections of either saline or AMPH (1 mg/kg, i.p.) following microinjections of either saline or CART 55-102 (2.5 μg/0.5μl/side) into this site. Accumbal CART 55-102 recovered the decreases of GSK3β and Akt phosphorylation back to saline levels. These results suggest that CART 55-102 peptide in the NAcc may play a compensatory inhibitory role in AMPH-induced locomotor activity by recovering the Akt-GSK3β signaling pathway modified by AMPH.

Disclosures: B. Cho: None. **W. Kim:** None. **J. Kim:** None.

Poster

779. Amphetamines: Mechanisms of Addiction and Sensitization

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Support: NSC 101-2320-B-182-040-MY3

Chang Gung Memorial Hospital CMRPD1D0291

Healthy Aging Research Center EMRPD1E1641

Title: Exploration of mTOR signaling in the ventral striatum during the development of methamphetamine sensitization

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Abstract: Behavioral sensitization to abused drug simulates human addicts that encode an array of obscure behaviors, however the molecular mechanism remains largely unclear. There are several cellular pathways may participate the progress of behavioral sensitization, and in this study we focus on change of mammalian target of rapamycin (mTOR) complex and down-stream regulator(s) in methamphetamine (METH) sensitized mice. Previous studies indicate that mTOR and its down-stream signals are important translation regulators in determining the neuroplasticity at synapse, however its impact on the progress of drug abuse is unclear. The aim of this study is to identify the role of mTOR signals in the development of METH sensitization in designated brain area. To this end, B6 mice were treated with daily METH (2 mg/kg, i.p.) for consecutive 8 days followed by behavioral monitoring. The results show that in METH sensitized mice, levels of total and phospho- mTOR/S2448 as well as its substrate phospho-p70S6K increased progressively along with daily METH injections in the ventral striatum, but not in dorsal striatum. The change of total mTOR could be also observed in a synaptosomal preparation from ventral striatum in METH-sensitized mice, suggesting a synaptic mTOR alteration. To examine the impact of mTOR up-regulation on METH sensitization, we co-administered mTOR inhibitor, rapamycin during daily METH injections and found mTOR inhibition significantly suppressed the degree of METH sensitization at behavioral initiation, but not expression stage. Further, via mTOR shRNA injection at ventral striatum, we confirm that decrease in mTOR expression suppressed behavioral sensitization to METH. These results suggest striatal mTOR plays an important role on initiation of METH sensitization.

Disclosures: **S. Huang:** None. **L. Lee:** None. **J. Chen:** None.

Poster

779. Amphetamines: Mechanisms of Addiction and Sensitization

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIH Intramural Research Program

Title: Genome-wide DNA hydroxymethylation patterns in the rat nucleus accumbens consequent to methamphetamine self-administration

Authors: *J. L. CADET[1], S. JAYANTHI[1], A. GODINO[1], I. KRASNOVA[1], M. T. MCCOY[1], B. LADENHEIM[1], O. TORRES[1], R. LEE[2];
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Abstract: In animal models of methamphetamine addiction, rats learn to self-administer the drug and accelerate their intake over time. However, these self-administration (SA) models do not include adverse psychosocial consequences that are embodied in the diagnostic criteria of substance use disorders. Indeed, adverse outcomes are relevant factors that can promote abstinence in humans. Here, we studied the genome-wide DNA hydroxymethylation consequences of suppression of drug seeking by repeated foot-shocks (punishment). Rats were trained to self-administer methamphetamine for 9 h per day for 20 days. Reward delivery was paired with a tone-light cue sequence. Subsequently, 50% of the lever-presses were punished by mild foot-shock for 10 days for one methamphetamine SA group whereas lever-presses were not punished for another methamphetamine SA group. Shock intensity (0.18-0.36 mA, 0.5 sec) was gradually increased over time. Response-contingent punishment suppressed extended-access methamphetamine taking in some rats (Punishment-sensitive, PS) whereas other rats were punishment-resistant (PR) and continued to press for methamphetamine at a high level. Rats were euthanized at 2 hours after the last self-administration session and brain regions were collected for further molecular experiments. Tissues from the nucleus accumbens (NAc) were used to identify differentially hydroxymethylated regions by using hydroxymethylated DNA immunoprecipitation followed by whole genome sequencing (hMeDIP-Seq). Our study identified several differentially hydroxymethylated regions in the NAc of methamphetamine self-administering rats. Several classes of genes showed differential DNA hydroxymethylation in rats that showed the PR compared to the PS phenotype. These included genes involved in epigenetic regulation (DNA methyl-transferase1-associated protein 1 and Sin3A), genes that code for protein phosphatases (protein phosphatase 1, regulatory subunit 12A), and several microRNAs (miRNA 146a). In comparison to the PS group, the PR phenotype also showed increased DNA hydroxymethylation at long interspersed nuclear elements (LINE), with these differences being potentially responsible for genomic instability and consequent altered gene expression in the PR rats. These observations are consistent with our previous suggestions that methamphetamine SA is associated with diverse molecular modifications in the brain. Our findings support the idea of developing specific epigenetic agents in order to expand the therapeutic armamentarium against methamphetamine addiction.

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Poster

779. Amphetamines: Mechanisms of Addiction and Sensitization

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Topic: C.17. Drugs of Abuse and Addiction

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Title: Efficacy of a tetanus-toxoid succinyl-methamphetamine vaccine differs between male and female mice

Authors: *T. A. KOSTEN[1,2,4], C. N. HAILE[1,2,4], K. J. WINOSKE[1], E. D. LYKISSA[5], N. NAIDU[5], B. M. KINSEY[3,4], R. ARORA[3,4], F. M. ORSON[4,3], T. R. KOSTEN[2,4]; [1]Psychology, Univ. of Houston, Houston, TX; [2]Psychiatry, [3]Immunol. Allergy & Rheumatology, Dept. of Med., Baylor Col. of Med., Houston, TX; [4]The Michael E DeBakey Veteran's Affairs Med. Ctr., Houston, TX; [5]ExperTox, Inc., Deer Park, TX

Abstract: Background: We previously reported that the behavioral effects of cocaine and response to an anti-cocaine vaccine significantly differed between male and female mice. Here we assessed potential sex differences in response to methamphetamine (MA). We also determined whether the efficacy of a vaccine targeting MA would show sex-dependent effects. The anti-MA vaccine was constructed of tetanus-toxoid linked to succinyl-methamphetamine (TT-SMA), absorbed with aluminum hydroxide, and administered with the adjuvant E6020, a Toll-like receptor-4 agonist. Methods: Locomotor activity was compared between male and female mice (BALB/c) following administration of various doses of MA (1-4mg/kg) in 90-min sessions. Separate groups of male and female mice, vaccinated with TT-SMA and boosted 3-weeks later, were employed to determine plasma anti-MA antibody concentrations at several time points across a 12-week period. Vaccinated and non-vaccinated female mice were administered MA (2.0mg/kg) and locomotor activity assessed. Brain levels were also evaluated in vaccinated and non-vaccinated mice 30-min following MA administration to assess whether the vaccine effectively decreased the ability of MA to cross the blood-brain barrier. Results: MA elicited greater locomotor activity in female compared to male mice at all doses tested (p's<0.05). Following vaccination, antibody levels increased after a boost at week 3 in both male and female mice; however, the increase was greater in female mice ($p<0.05$). Female mice vaccinated with SMA-TT showed attenuated MA-induced locomotor activation (2.0mg/kg; $p<0.05$) and significantly lower brain levels of MA compared to non-vaccinated female mice ($p<0.001$). Conclusions: Results suggest female mice are more sensitive to the locomotor activating effects of MA and to the immunogenicity of the TT-SMA vaccine. That the vaccine attenuated

MA-induced locomotor activation is likely due to slowing MA brain penetration and supports the future development of this vaccine construct for the treatment of MA addiction, particularly in female addicts.

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Poster

779. Amphetamines: Mechanisms of Addiction and Sensitization

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Title: Methamphetamine reward: contribution of toll-like receptor 4 and proinflammatory mediators

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Abstract: Drug reward has long been attributed to neuronal responses, chiefly within the mesolimbic dopamine (DA) pathway. Recent evidence suggests that glial activation within the brain is also required for drug reward. Morphine and cocaine activate glial Toll-Like Receptor 4 (TLR4), resulting in proinflammatory, neuroexcitatory signaling. TLR4 is an innate immune pattern recognition receptor, expressed principally on microglia in the CNS. TLR4 appears to recognize morphine and cocaine as xenobiotics (i.e., substances foreign to the brain), triggering

CNS glial signaling, akin to the immune responses elicited by bacteria. The ensuing proinflammatory cascade can have neuroexcitatory consequences. In the case of morphine or cocaine, blockade of TLR4; 1) prevents induction of CNS immune activation, 2) suppresses conditioned place preference (CPP), 3) blocks drug-induced DA increases within the nucleus accumbens (NAc) and 4) attenuates drug self administration. These findings indicate that drug-induced proinflammatory CNS glial signaling is necessary for drug reward and reinforcement. Methamphetamine (METH) is thought to exert its rewarding effects via reversal of DA transporters in the mesolimbic DA pathway. Repeated METH use is also associated with neurotoxicity. There are indications that CNS glial activation may contribute to METH's rewarding and neurotoxic effects. However, the mechanism by which METH triggers a CNS glial response is unknown. Here, we show that METH can bind to TLR4 to initiate glial reactivity. Systemic METH TLR4-dependently induces upregulation of proinflammatory markers in the brain, notably within the ventral tegmental area (VTA). Systemic TLR4 antagonism also attenuates METH CPP and METH-induced increases of DA within the NAc. We recently demonstrated that the rewarding effects of cocaine are dependent on IL1β signaling within the VTA. METH also initiates CNS glial responses within the VTA. However, intra-VTA mRNA is upregulated for IL6 but not IL1β at the timepoints tested. Studies are currently underway to investigate whether METH-induced NAc DA increases and METH self-administration are dependent on intra-VTA IL6 signaling. Interestingly, IL6 has been linked to METH neurotoxicity, suggesting a role for METH-induced CNS glial signaling underlying both reinforcement and neurotoxicity. Our data suggest that METH-activation of TLR4 contributes to its rewarding effects, as well as implicating a possible mechanism underlying neurotoxicity. These findings provide further support for the xenobiotic hypothesis, and indicate that TLR4 may be a promising target for pharmacological intervention to treat drug abuse.

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Poster

779. Amphetamines: Mechanisms of Addiction and Sensitization

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R01NS071122-A1

S10OD020026

Title: Alpha-synuclein elevation shapes dopamine neurotransmission via a DAT dependent mechanism

Authors: *K. SAHA[1], B. BUTLER[1], M. LIN[1], R. STEGER[1], J. COLEMAN[2], B. GIASSON[1], T. E. GOLDE[1], H. KHOSHBOUEI[1];
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Abstract: Alpha-synuclein is a small cytosolic protein enriched in the presynaptic terminals. Although its physiological function remains unknown, alpha-synuclein has been implicated in a number of pathological conditions coined synucleinopathies, which include Parkinson's disease. Though, the neuroprotective and/or neurotoxic effects of endogenous levels of alpha-synuclein is debated, it is clear that pathological levels of alpha-synuclein negatively affects the activity of dopaminergic neurons, albeit with less understood mechanism. Here we examined whether overexpression of wild-type alpha-synuclein influences the activity of dopamine neurons by measuring the spontaneous firing activity and action potential morphology of dopamine neurons. Electrophysiological results revealed that alpha-synuclein elevation decreases the frequency of spontaneous firing of dopamine neurons, increases action potential half-width and reduces afterhyperpolarization (AHP) magnitude. Alpha-synuclein overexpression enhances the action potential half-amplitude following amphetamine (AMPH) exposure compared to neurons expressing physiological levels of alpha-synuclein. We used GCaMP6, a highly sensitive calcium sensor, to study calcium dynamics in the neuronal cell bodies and processes when alpha-synuclein is overexpressed. In the absence of stimulation, as compared to control neurons containing endogenous alpha-synuclein levels, alpha-synuclein over-expression increased calcium spike amplitude and decreased spike frequency in neuronal cell bodies, but not in the neuronal process. Since activation of dopamine transporter (DAT) has been shown to increase intracellular calcium, we asked whether alpha-synuclein regulation of intracellular calcium is DAT dependent. We found alpha-synuclein regulation of calcium mobilization in the cell body and neuronal processes was blocked by inhibition of dopamine transporter; whereas, amphetamine activation of DAT further enhanced the calcium spike amplitude in both the neuronal cell bodies and processes that overexpressed alpha-synuclein. These preliminary data suggest alpha-synuclein elevation uniquely impacts dopamine neurotransmission via a DAT-dependent mechanism.

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Poster

779. Amphetamines: Mechanisms of Addiction and Sensitization

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Topic: C.17. Drugs of Abuse and Addiction

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NIDA Drug Inventory Supply and Control

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The University of Texas VP Research Office

Title: Preferential enhancement of MDMA-induced accumbens 5-HT over DA levels is amplified by 5-HT2C receptor antagonism

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Abstract: Actions on serotonin (5-HT) and dopamine (DA) systems underlie unique behavioral and neurochemical responses induced by 3, 4-methylenedioxymethamphetamine (MDMA or "Ecstasy"). 5-HT receptors can modulate 5-HT and DA function, but their specific role in MDMA-induced effects are yet to be determined. This study was conducted to investigate the effects of 5-HT2c receptor antagonism on MDMA-induced changes in nucleus accumbens (NAcc) extracellular 5-HT and DA levels, locomotor activity and spontaneous behaviors. During a 2-h *in vivo* microdialysis test session, MDMA-naïve rats were treated with either saline (0.2 ml) or the 5-HT2C selective antagonist, SB 242084 (1.0 mg/kg, i.v.) 30-min prior to a self-administered infusion of MDMA (3.0 mg/kg, i.v.) or saline (0.1 ml). Saline pretreated rats showed pronounced increases in NAcc extracellular 5-HT (approx 5-fold) and DA (approx 2-fold) after MDMA administration. Pretreatment with SB 242084 resulted in significantly enhanced extracellular NAcc 5-HT (approx 9.5-fold) and behaviors associated with serotonin syndrome (e.g., low body posture, forelimb and hindlimb treading) after MDMA injection. MDMA-stimulated NAcc DA and locomotor activity was comparable in SB 242084 and saline pretreated animals and SB 242084 alone did not alter NAcc 5-HT, DA or behavioral activities prior to MDMA administration or after saline injection. Our findings indicate that 5HT2C receptor antagonism in combination with MDMA preferentially amplifies MDMA-induced NAcc 5-HT neuronal and behavioral responses compared to NAcc DA and DA-mediated effects.

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Poster

779. Amphetamines: Mechanisms of Addiction and Sensitization

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Title: PKC-b inhibitors attenuate amphetamine and cocaine stimulated dopamine release

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Abstract: Amphetamine abuse afflicts over 13 million people, and there is currently no universally accepted treatment for amphetamine addiction. Amphetamine serves as a substrate for the dopamine transporter (DAT) and reverses the transporter to cause dopamine efflux in addition to inhibiting the vesicular monoamine transporter (VMAT) to promote dopamine exocytosis. Activation of protein kinase Cb enhances extracellular dopamine in the presence of amphetamine by enhancing the reverse transport of dopamine and internalizing the D2 autoreceptor. We previously demonstrated that PKCb inhibitors block amphetamine-stimulated dopamine efflux in rat striatum *in vitro*. In this study, we utilized *in vivo* microdialysis in live, behaving rats to assess the effect of the PKCb inhibitors enzastaurin and ruboxistaurin on amphetamine-stimulated increases in monoamines and their metabolites. A 30 min perfusion of the nucleus accumbens core with 1 uM enzastaurin or 1 uM ruboxistaurin reduced amphetamine-stimulated efflux of dopamine and its metabolite 3-methoxytyramine by approximately 50%. The inhibitors also significantly reduced extracellular levels of norepinephrine and its metabolite normetanephrine after amphetamine. The stimulation of locomotor behavior by amphetamine, measured simultaneously with the analytes, was comparably reduced by the PKCb inhibitors. Ruboxistaurin also attenuated cocaine stimulated extracellular dopamine, a process that would not be dependent upon DAT reversal. In order to see if this process was D2 autoreceptor mediated, we examined the effect of ruboxistaurin on cocaine activation when D2 receptors were blocked with raclopride. The inhibitory effect of ruboxistaurin was reduced in the presence of

cocaine and raclopride, suggesting that ruboxistaurin action involved D2 autoreceptors. Using a stable isotope label retrodialysis procedure, we determined that ruboxistaurin had no effect on basal levels of dopamine, norepinephrine, glutamate, or GABA. Our results support the utility of using PKCb inhibitors to reduce the effects of amphetamine and cocaine.

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Poster

779. Amphetamines: Mechanisms of Addiction and Sensitization

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NARSAD Young Investigator Award

Title: Amphetamine sensitization requires dopamine neuron glutamate cotransmission

Authors: *S. MINGOTE[1], N. CHUHMA[1], A. KALMBACH[1], A.-C. SIENA[1], B. INBAR[2], H. MOORE[2], S. RAYPORT[1];
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Abstract: Increased activity of dopamine (DA) neurons projecting to the nucleus accumbens (NAc) shell is thought to mediate the initial reinforcing effects of abused drugs such as amphetamine (Covey et al., TINS, 2014). Mesoaccumbal DA neurons are distinguished by showing the highest incidence of glutamate (GLU) cotransmission; however it is not clear whether DA neuron GLU cotransmission is involved in the development of drug-induced responses. Transgenic approaches have abrogated GLU cotransmission by conditional knock out of the vesicular GLU transporter VGLUT2 in DA neurons; VGLUT2 cKO mice show a reduced response to amphetamine, but this could be due to reduced DA or GLU release (Birgner et al., PNAS, 2010), as VGLUT2 cKO mice also have reduced DA neuron numbers, DA content and release (Hnasko et al., Neuron, 2010; Fortin et al., JNS, 2012). To address the role of DA neuron GLU cotransmission specifically, we targeted GLS1, which encodes the GLU synthetic enzyme

glutaminase that mediates glutamate recycling and is important for maintaining GLU neurotransmission at fast firing frequencies. Unlike VGLUT2 cKO mice, GLS1 cHet mice (with a conditional heterozygous deletion of GLS1 in DA neurons) showed no alteration in DA content, DA release or DA neuron number. This allowed us to focus on the contribution of high frequency DA neuron GLU cotransmission, specifically during burst firing. We have recently shown that stimulation of DA neurons at burst firing frequencies can drive cholinergic interneurons (ChIs) in the NAc shell to burst fire, and that after a single dose of amphetamine, these DA neuron excitatory connections undergo a dramatic drug-induced plasticity (Chuhma et al., Neuron, 2014). We have now found, in DAT- IREScre::Ai32 mice and recording in ChIs, that photostimulation of DA neuron terminals elicits GLU cotransmission that shows more rapid frequency dependent attenuation in GLS1 cHet (triple mutant) mice. Consistent with the overall lack of impact on DA transmission, GLS1 cHet mice showed no motor impairments measured on the rotarod, nor an altered dose-response curve for amphetamine-induced locomotion. Strikingly, GLS1 cHet mice did not show sensitization to repeated amphetamine. Thus, DA neuron GLU transmission at burst firing frequencies appears to underlie the development of drug-induced behaviors.

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Poster

779. Amphetamines: Mechanisms of Addiction and Sensitization

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Title: Phosphorylation by PKC of the GluA1 subunit of the AMPA receptor in the nucleus accumbens is required for the expression of amphetamine sensitization

Authors: *V. KONDEV, D. LI, N. BUBULA, P. VEZINA;
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Abstract: Two experiments assessed the contribution of PKC phosphorylation in the nucleus accumbens (NAcc) to the expression of locomotor sensitization by amphetamine. PKC constitutes a family of serine-threonine kinases that can be classified into three main isozyme subgroups with numerous substrates in the central nervous system. Some of these substrates

especially in the NAcc could play a role in the expression of sensitization by amphetamine. In the first experiment, rats in different groups were exposed to 5 injections of amphetamine (1.5 mg/kg, IP; 1 injection every other day) and three weeks later, challenged with saline or amphetamine (1.0 mg/kg, IP). NAcc tissues were harvested 30 minutes later and PKC activity determined with a PepTag non-radioactive PKC assay using PLSRTLSVAAK as peptide substrate or pNeurogranin(S36) as a postsynaptic endogenous substrate. In both cases, amphetamine exposure did not affect basal PKC activity but did enhance activity levels observed following the amphetamine challenge, suggesting a role for this kinase in the expression of locomotor sensitization by amphetamine. To further characterize this role, a second experiment assessed the need for phosphorylation by PKC of the S816-S818 residues of the GluA1 subunit of AMPA receptors in the NAcc. Phosphorylation of these residues is known to facilitate GluA1 insertion into the plasma membrane which in turn can enhance glutamatergic transmission and amphetamine-induced locomotion. Rats in different groups were exposed to saline and amphetamine as above. One week later, they were infected in the NAcc with lentivirus bearing GFP or the serine-alanine mutant GluA1(S816A-S818A) and two weeks after that tested for their locomotor response to NAcc amphetamine (2.5μg/side). Preventing GluA1 phosphorylation with the serine-alanine mutant blocked expression of the sensitized locomotor response to NAcc amphetamine normally observed in amphetamine exposed rats. Together, these results support the need for NAcc PKC in the expression of behavioral sensitization by amphetamine and highlight the importance of NAcc AMPA receptor regulation by PKC in generation of the sensitized response.

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Poster

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIH grant R01 DA09397.

Title: Exposure to amphetamine enhances AMPA receptor phosphorylation by CaMKII without increasing cell surface expression

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Abstract: While exposure to either cocaine or amphetamine leads to various manifestations of sensitization, only exposure to cocaine has been found to produce long-lasting increases in basal cell surface and synaptic AMPA receptor (AMPAR) levels in rat forebrain. This led us to further characterize changes in AMPAR expression in the nucleus accumbens (NAcc) long after amphetamine exposure. In a first series of experiments using the BS3 cross-linking approach, no difference between saline and amphetamine exposed rats was found in the cell surface expression of either GluA1 or GluA2 AMPAR subunits. This finding was supported in a second experiment showing no difference between these two groups in the amplitude of AMPAR-mediated mEPSCs recorded in NAcc slices. This finding was again confirmed in a third experiment showing no effect of amphetamine exposure in GluA1 and GluA2 levels observed either in whole cell lysate or in the PSD of NAcc neurons subjected to subcellular fractionation and Western blot assays. On the other hand and extending previous findings obtained in whole cell lysates, we found in a fourth experiment conducted in PSD fractions of NAcc shell tissues that exposure to amphetamine produces a long-lasting increase in pGluA1(S831), a CaMKII residue. This increase in GluA1 phosphorylation was accompanied by a significant and long-lasting increase in levels of CaMKIIα, but not CaMKIIβ, in PSD fractions of the NAcc shell. This enrichment of CaMKIIα in the PSD may provide one mechanism for the enduring increase in pGluA1(S831) which in turn can contribute to the enhanced behavioral responding to amphetamine and NAcc AMPA observed in sensitized rats. Finally, in an effort to delineate a mechanism underlying the increase in PSD CaMKIIα, a fifth experiment using immunoprecipitation assessed the effect of amphetamine exposure on changes in protein coupling in the PSD. Interestingly, previous exposure to amphetamine was found to modestly increase the coupling of CaMKIIα to PSD-95 but to significantly decrease CaMKIIα/NR2b and increase NR2b/PSD95 coupling. Overall, these results reveal significant changes in protein interactions in the PSD of NAcc medium spiny neurons that are well positioned to influence AMPAR mediated signaling underlying the expression of behavioral sensitization by amphetamine. Some of the changes observed in protein coupling in the PSD are surprising given the need for increased CaMKIIα/NR2b coupling in the expression of LTP. The decrease in CaMKIIα/NR2b coupling observed in the present experiments likely characterizes a basal interactive state between these two proteins in periods removed from amphetamine challenge.

Disclosures: Q. Wang: None. **D. Li:** None. **N. Bubula:** None. **M. Campioni:** None. **D.S. McGehee:** None. **P. Vezina:** None.

Poster

779. Amphetamines: Mechanisms of Addiction and Sensitization

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 779.18/I43

Topic: C.17. Drugs of Abuse and Addiction

Support: FONDECYT Grant 3130683

Title: Amphetamine modulates Nurr1 and NF-kB p65 expression in the rat Ventral Tegmental Area

Authors: *C. ARREDONDO, M. P. GONZÁLEZ, M. E. ANDRÉS, K. GYSLING;
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Abstract: Psychostimulants are drugs with high consumption rates worldwide, resulting in a major public health problem. The rewarding and addictive effects of drugs of abuse are produced by increased dopaminergic neurotransmission in the ventral midbrain area and its target nuclei. Nurr1 is a nuclear receptor essential for the development and survive of midbrain dopaminergic neurons. This transcription factor regulates the expression of key genes of the dopaminergic phenotype as tyrosine hydroxylase (TH) and dopamine transporter. It is well known that repeated consumption of drugs of abuse causes long-lasting changes in dopaminergic neurons. The evidence also points to abused drugs as triggers of inflammatory processes and damage in the brain. Exposure to cocaine and methamphetamine alters the transcription factor NF-kB levels in PC12 cells. Interestingly, Nurr1 and NFkB-p65 interact to regulate inflammatory genes in response to lipopolysaccharide (LPS) in microglia and astrocytes. The objective of this work was to study the changes in Nurr1, NFkB-p65 and TH expression in the rat midbrain region, after an acute and chronic exposure to amphetamine. Male Sprague-Dawley rats weighing about 280g were injected with amphetamine (1.5 mg/kg) acutely or every day during fourteen days (chronic). Our data show that Nurr1 and NFkB-p65 co-localize in TH-positive cells in the rat ventral tegmental area. Nurr1, TH and NFkB-p65 expression was assessed by Western blots of ventral midbrain total protein extracts. Acute amphetamine treatment induced an increase in Nurr1, TH and NFkB-p65 protein levels. Chronic amphetamine treatment decreased Nurr1 and NFkB-p65 protein levels, but TH was unchanged compared to saline-treated rats. Our results show that Nurr1 in midbrain dopaminergic neurons responds in a different way to acute or chronic amphetamine treatment and suggest that Nurr1 and NFkB-p65 could mediate a common response to amphetamine

Disclosures: C. Arredondo: None. **M.P. González:** None. **M.E. Andrés:** None. **K. Gysling:** None.

Poster

779. Amphetamines: Mechanisms of Addiction and Sensitization

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Comunidad de Madrid ref. S2011/BMD-2336

CONACYT-Mexico postdoctoral scholarship to L Mendieta (208063)

Title: Fragment C domain of tetanus toxin mitigates methamphetamine neurotoxicity and its motor consequences in mice

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Abstract: The C-terminal domain of the heavy chain of tetanus toxin (Hc-TeTx) is a nontoxic peptide with demonstrated *in vitro* and *in vivo* neuroprotective effects against striatal dopaminergic damage induced by MPP+ (1-methyl-4-phenylpyridinium) and 6-hydoxydopamine, suggesting its possible therapeutic potential in Parkinson's disease. Methamphetamine (METH), a widely abused psychostimulant, has selective dopaminergic neurotoxicity in rodents, monkeys and humans. This study was undertaken to determine whether Hc-TeTx might also protect against METH-induced dopaminergic neurotoxicity and the consequent motor impairment. For this purpose, we treated mice with a toxic regimen of METH (4 mg/kg, 3 consecutive i.p. injections, 3h apart) followed by 3 injections of 40 ug/kg of Hc-TeTx into grastrocnemius muscle at 1h, 24h and 48h post METH treatment. We found that Hc-TeTx significantly reduced the loss of dopaminergic markers tyrosine hydroxylase (TH) and dopamine transporter (DAT) and the accompanying increases in silver staining (a well established degeneration marker) induced by METH in the striatum at 3 and 7 days after METH

treatment. Moreover, Hc-TeTx prevented the increase of neuronal nitric oxide synthase (nNOS), but did not affect microglia activation induced by METH. Stereological neuronal count in the substantia nigra indicated loss of TH-positive neurons after METH that was not significantly affected by Hc-TeTx. Importantly, impairment in motor behaviors on days 1 and 3 post METH treatment, were significantly reduced by Hc-TeTx. Here we demonstrate that Hc-TeTx can provide significant protection against METH-induced neurotoxicity and motor impairment. Thus, Hc-TeTx fragment may represent a potential therapeutic drug for METH-abusers.

Disclosures: L. Martinez Mendieta: None. **N. Granado:** None. **J. Aguilera:** None. **Y. Tizabi:** None. **I. Limón:** None. **R. Moratalla:** None.

Poster

779. Amphetamines: Mechanisms of Addiction and Sensitization

Location: Hall A

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Program#/Poster#: 779.20/I45

Topic: C.17. Drugs of Abuse and Addiction

Support: R01 DA033436

Title: Antisense-mediated downregulation of xCT reduces basal glutamate in the NA and alters post-synaptic AMPA receptor subunit expression

Authors: *A. L. LACROSSE[1], M. A. GORDON[2], B. S. JACKSON[2], L. A. KNACKSTEDT[2]; [1]Psychology, [2]Univ. of Florida, Gainesville, FL

Abstract: Ceftriaxone is a beta-lactam antibiotic which increases the expression and function of the glutamate transporter GLT-1 and of system xC-, which exchanges extracellular cysteine for intracellular glutamate. Basal glutamate levels in the NA (NA) are largely controlled by system xC-, and a decrease in its activity is a contributing cause of the altered glutamate homeostasis observed in this brain region following cocaine self-administration in rats. The catalytic subunit of xC- is xCT, and we have demonstrated that expression of xCT and GLT-1 is decreased in the NA core following cocaine self-administration. We have also shown that ceftriaxone attenuates cue- and cocaine-primed reinstatement while restoring levels of both xCT and GLT-1 in the NA core. At this time it is not known if alterations in both transport systems mediate the altered synaptic plasticity in the NA after cocaine self-administration. Here we used a morpholino antisense strategy to decrease the expression of xCT protein and examined basal levels of glutamate and GluA1 and GluA2 expression. We found that xCT antisense infusion into the NA significantly decreased basal glutamate. We also found an increase in NA GluA1 expression in

cocaine self-administering rats and no change in GluA2 expression. In ceftriaxone-treated rats infused with xCT antisense in the NA, this increase in GluA1 was potentiated. These data support the importance of xCT expression in maintaining basal glutamate in the nucleus accumbens and point to basal glutamate levels as a key mediator of post-synaptic AMPA receptor alterations.

Disclosures: A.L. LaCrosse: None. **M.A. Gordon:** None. **B.S. Jackson:** None. **L.A. Knackstedt:** None.

Poster

779. Amphetamines: Mechanisms of Addiction and Sensitization

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: C.17. Drugs of Abuse and Addiction

Title: Role of the ribosomal protein S6 phosphorylation in the mouse brain

Authors: *A. BIEVER[1], E. PUIGHERMANAL[1], V. PASCOLI[2], O. MEYUHAS[3], C. LÜSCHER[2], E. VALJENT[1];
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Abstract: The 40S subunit ribosomal protein S6 (rpS6) has attracted much attention over the last four decades since it is the first ribosomal protein shown to undergo inducible phosphorylation upon a wide variety of stimuli. However, despite the profound elucidation of the respective kinases and extracellular stimuli triggering phospho-rpS6, little is known about the physiological role of its phosphorylation. In this study, we aimed to characterize the functional relevance of the *in vivo* rpS6 phosphorylation in the brain. For this purpose, we performed a behavioral characterization of rpS6P-/- knock-in mice, in which all phosphorylatable serine residues are substituted by alanines. Interestingly, these mice display a reduced locomotor response to d-amphetamine, which markedly increases phospho-rpS6 in the striatum of wild-type mice. Moreover, they show impaired synaptic plasticity of GABAergic medium-sized spiny neurons in the nucleus accumbens. Finally, since rpS6 phosphorylation has been widely correlated with changes in protein synthesis, we performed polysome profile and puromycin incorporation analyses in rpS6P-/- knock-in as well as in wild-type mice treated with d-amphetamine. Intriguingly, we found no differences in global translational rates in the striatum, hippocampus and frontal cortex. Altogether, our results indicate that neither basal nor drug-induced transient rpS6 phosphorylation correlate with changes in overall mRNA translation. Nevertheless, despite

the lack of causal relationship between both events, rpS6 phosphorylation plays an important role in striatal plasticity and behavioral responses.

Disclosures: **A. Biever:** None. **E. Puighermanal:** None. **V. Pascoli:** None. **O. Meyuhas:** None. **C. Lüscher:** None. **E. Valjent:** None.

Poster

780. Translational Studies of Treatments for Addiction

Location: Hall A

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Program#/Poster#: 780.01/I47

Topic: C.17. Drugs of Abuse and Addiction

Support: R01DA035240-01

Title: Predicting treatment outcome in prescription opiate dependence using functional near infrared spectroscopy (fnir)

Authors: ***A. HUHN**[1], S. C. BUNCE[2], D. STANKOSKI[2], J. HARRIS[2], E. BIXLER[2], R. E. MEYER[2];
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Abstract: Aims: Growing evidence for a neuroadaptive model underlying long-term vulnerability to relapse in opiate dependence is largely based on animal research; little is known about its predictive capability concerning risk of relapse in clinical populations. The period directly following opiate withdrawal is marked by heightened CNS response to drug-related stimuli, diminished pleasure from natural rewards, increased stress response and irritability. The current study utilizes a cue reactivity paradigm coupled with fNIR to test the hypothesis that recently withdrawn prescription opiate dependent patients (RWP) in a residential setting would show reduced response to natural rewards and heightened response to drug-related stimuli. To date, relapse information has been gathered from a subset of patients, allowing us to examine the predictive value of this data. Methods: RWP (n=11) and healthy controls (HC; n=8) were evaluated using fNIR as they viewed hedonically positive (food), socially-relevant positive, drug related, or neutral stimuli. RWPs data was collected in a residential treatment facility, 10-14 days after withdrawal. T-tests and Pearson's correlations were used to compare fNIR response across groups. Results: RWPS showed reduced bilateral response to natural reward stimuli in the dorsolateral PFC (DLPFC) relative to HC ($p<.05$). Outcome data were available from a subgroup of RWP (n=8) that had either relapsed (n=4) or remained abstinent (n=4) for a period of three months following discharge from residential treatment. Relapse was associated with increased

activation in the right DLPFC ($p<.05$) in response to food and drug stimuli, and decreased activation ($p<.01$) in bilateral DLPFC and ventromedial PFC in response to socially rewarding stimuli. Responses to drug stimuli and socially rewarding were negatively correlated ($r=-.727$; $p=.041$) Conclusion: Consistent with previous studies, these data suggest RWPs display differential CNS responses to natural reward cues relative to HCs. Importantly, these preliminary data suggest that CNS responses in the PFC may serve as a biomarker to predict treatment outcome; this has the potential to be a powerful tool for clinicians (e.g., as an objective measure of vulnerability to relapse to guide treatment planning). These data demonstrate the feasibility of using fNIR, a relatively low-cost neuroimaging tool, in translational care.

Disclosures: **A. Huhn:** None. **S.C. Bunce:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); fNIR Devices LLC. **D. Stankoski:** None. **J. Harris:** None. **E. Bixler:** None. **R.E. Meyer:** None.

Poster

780. Translational Studies of Treatments for Addiction

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIDA Grant 1 R01 DA020870-01

NIAAA Grant 1 T32 AA018108-01A1

Title: Functional magnetic resonance imaging measures of network connectivity related to incorrect responses predict completion of substance abuse treatment

Authors: *V. R. STEELE[1], E. D. CLAUS[2], B. C. FINK[3], J. M. MAURER[1], M. R. ARBABSHIRANI[2], V. RAO[2], V. D. CALHOUN[1], K. A. KIEHL[1];
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Abstract: US nationwide estimates indicate at least two-thirds of prisoners have a history of substance abuse or dependence. Tailoring substance abuse treatment to specific needs of incarcerated individuals could improve effectiveness of treating substance dependence and preventing drug abuse relapse. The purpose of the present study was to test the hypothesis that pre-treatment functional connectivity measures of error processing would predict which individuals would or would not complete a 12-week cognitive behavioral substance abuse

treatment program. Adult incarcerated participants (N = 139; Females = 89) who volunteered for substance abuse treatment performed a response inhibition (Go/NoGo) functional magnetic resonance imaging (fMRI) task. Independent component analysis (ICA) was performed to identify networks related to false alarms elicited during the Go/NoGo task. Functional network connectivity measures of ICs related to false alarms were used to classify individuals who completed (N = 107; Females = 75) and discontinued (N = 32; Females = 14) treatment. A support-vector machine (SVM) classifier with a double input symmetric relevance feature selection step was used to identify two functional network connections that predicted treatment completion and discontinuation. For cross-validation, a nested 5-fold SVM with a radial basis function kernel was used to produce an overall accuracy of 81% while also identifying 81% of individuals who completed and 78% who prematurely discontinued treatment. Increased connectivity between the rostral anterior cingulate cortex (RACC) and striatal regions was measured in the completed group compared to the discontinued group. Increased connectivity between the caudal anterior cingulate cortex (CACC) and temporal regions (including insula) was measured in the discontinued group compared to the discontinued group. These findings support previous event-related potential (ERP) effects highlighting deficiencies in error-monitoring and post-error response adjustments in individuals who prematurely discontinue treatment. Cross-modal similarities suggest future treatments could be refined by targeting error-monitoring and post-error response adjustment in at-risk individuals, which could lead to more favorable long-term outcomes.

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Poster

780. Translational Studies of Treatments for Addiction

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: C.17. Drugs of Abuse and Addiction

Support: RAS, Region Autonoma della Sardegna, Italy - LR 7/2007

Title: Effects of withania somnifera dunal (indian ginseng) on morphine- and ethanol-induced motivation in rodents

Authors: *E. ACQUAS[1], M. ROSAS[2], L. SPINA[2], S. RUIU[5], A. ORRU'[6], A. T. PEANA[7], M. COLLU[3], F. COTTIGLIA[4], S. B. KASTURE[8];
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Cagliari, CAGLIARI, Italy; [4]Dept. of Life and Envrn. Sci., Univ. of Cagliari, Cagliari, Italy; [6]Inst. of Translational Pharmacology, UO Cagliari, [5]Italian Natl. Res. Council, Pula (Cagliari), Italy; [7]Chem. and Pharm., Univ. of Sassari, Sassari, Italy; [8]Sanjivani_College_of_Pharmaceutical_Education_Research, Kopargaon, India, Kopargaon, India

Abstract: The standardized roots extract of Withania somnifera Dunal, a medicinal plant mostly used for its anti-inflammatory properties, has been shown to interact with a number of morphine and ethanol central effects. Thus, it has been shown that Withania prevents ethanol withdrawal-induced anxiety, potentiates ethanol-induced anxiolysis and prevents development of tolerance to the analgesic effects of morphine. In addition, we also reported that chronic administration of WSE prevents the loss of dendritic spines that takes place in the nucleus accumbens shell upon morphine withdrawal in morphine-dependent rats. As an extension of these observations, the aim of our work was investigating further the effects of Withania somnifera roots extract (WSE) on morphine-elicited conditioned place preference (CPP) and ethanol-elicited place conditioning (both preference (CPP) and aversion (CPA)) and on motivation for drinking ethanol by operant self-administration (SA) paradigms. To this end, in morphine CPP experiments male CD-1 mice underwent backward conditioning (CPP) whereas in ethanol conditioning experiments mice underwent both backward and forward (CPA) conditioning; the effects of WSE (50 and 100 mg/kg) were evaluated on acquisition and expression of both morphine- and ethanol-elicited conditioning. In self-administration experiments male Wistar rats were trained to self-administer ethanol (10%) by nose-poking and the effects of WSE (25 - 75 mg/kg) were evaluated on acquisition and maintenance of ethanol self-administration, on ethanol breakpoint under a progressive-ratio schedule of reinforcement, on ethanol deprivation effect and on reinstatement of seeking behaviours. The results of these experiments confirmed 1) that under appropriate experimental conditions, morphine and ethanol elicit place conditioning; 2) that the administration of WSE dose-dependently impairs both the acquisition and the expression of morphine-elicited CPP and of ethanol-elicited CPP and CPA; 3) that WSE reduces acquisition, maintenance and breakpoint of ethanol self-administration as well as the deprivation effect and reinstatement of ethanol-seeking behaviour. Although further studies are required to investigate in detail the mechanism(s) by which WSE interferes with the motivational properties of morphine and ethanol, these results provide strong support to the suggestion that the use of WSE could represent an interesting phytotherapeutic approach.

Disclosures: E. Acquas: None. **M. Rosas:** None. **L. Spina:** None. **S. Ruiu:** None. **A. Orru':** None. **A.T. Peana:** None. **M. Collu:** None. **F. Cottiglia:** None. **S.B. Kasture:** None.

Poster

780. Translational Studies of Treatments for Addiction

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIH grant K08-GM-093115

NIMH PDSP; Contract # HHSN-271-2008-00025-C

Title: Dezocine and buprenorphine reduces withdrawal syndrome in a morphine dependent rat model

Authors: *R. LIU[1], F.-X. WU[1], C.-H. CHUN-HUA XI[1], X.-P. HUANG[3], J. MA[2], W. YU[4], B. ROTH[3];
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Abstract: Opioid dependence continues to be a major public health issue without optimal therapeutic. Based on our recent discovery of the unique pharmacological profile of dezocine as a non-addictive opioid, a partial mu agonist and kappa antagonist, similar to that of buprenorphine, we hypothesized that dezocine could be used to manage opioid dependence. In the present study, the effects of dezocine and buprenorphine on morphine withdrawal syndrome were compared in a rat morphine dependence model. Daily intraperitoneal injection of dezocine markedly reduced morphine withdrawal syndrome similar to that of buprenorphine. Astrocyte activation in nucleus accumbens after opioid exposure was observed in the morphine dependent rats, and such astrocyte activation was significantly inhibited in the presence of dezocine and buprenorphine. The molecular target profiling for both dezocine and buprenorphine was performed. Dezocine interact with sigma 1 receptor, while buprenorphine has no interaction with sigma 1 receptor. These findings suggested that dezocine could be an alternative medication for opioid addiction management similar to that of buprenorphine. The advantage of dezocine over buprenorphine for opioid dependence management is proposed.

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Poster

780. Translational Studies of Treatments for Addiction

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Topic: F.02. Animal Cognition and Behavior

Support: Grant

Title: Characterizing molecular mechanisms of adolescent cue exposure therapy in animal models of addiction and anxiety

Authors: *I. ZBUKVIC, D. GANELLA, C. BYE, C. PERRY, H. MADSEN, A. LAWRENCE, J. KIM;
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Abstract: Substance abuse and anxiety disorders represent two of the most common mental illnesses worldwide, with onset most often occurring during adolescence. Treatment for these disorders frequently involves cue exposure therapy (CET), based on the principle of cue extinction. This type of learning is known to involve dopamine signaling in the prefrontal cortex (PFC), a system undergoing dramatic alterations during adolescence. These changes may result in a deficit in cue extinction learning, which would explain adolescent resistance to treatment such as CET in the clinical setting. The present study aimed to characterize CET in adolescent versus adult rats using a cocaine self-administration paradigm and a fear conditioning paradigm. In the first study, adolescent and adult rats were trained to lever press for cocaine (3mg/kg/infusion) over 10-12 days, where cocaine infusions were paired with a light cue. Once stable self-administration was established, rats received 7 daily lever extinction sessions, where lever pressing had no programmed consequences. The following day rats underwent a single cue extinction session designed to model CET consisting of 120 cue-alone presentations, or remained in their home cages. Cue extinction significantly reduced cue-induced reinstatement next day in adult but not adolescent rats ($p<.05$). We then measured changes in dopamine receptor mRNA expression in the PFC and the striatum following cocaine-associated cue extinction. In the second study, adolescent and adult rats were fear conditioned using 3 tone-footshock pairings. The next day rats underwent a single cue extinction session designed to model CET consisting of 30 presentations of the tone in absence of the footshock. Cue extinction significantly reduced reinstatement of conditioned fear the next day in adult rats only ($p<.05$). We then measured changes in dopamine receptor mRNA expression in the PFC and the amygdala following cue extinction.

Disclosures: I. Zbukvic: None. **D. Ganella:** None. **C. Bye:** None. **C. Perry:** None. **H. Madsen:** None. **A. Lawrence:** None. **J. Kim:** None.

Poster

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Topic: C.17. Drugs of Abuse and Addiction

Support: SIP-IPN 20141077

INPRFM NC103380.2

Estimulos Fundacion Miguel Aleman 2013

Title: Effect of environmental enrichment on glutamate concentrations in the hippocampus and prefrontal cortex in mice exposed to toluene

Authors: *N. PAEZ-MARTINEZ[1,2], R. SOLIS-GUILLEN[1], S. MONTES-LOPEZ[3];
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Abstract: Inhalants are substances widely used as recreational drugs. These are easy to obtain in legal, relatively inexpensive and common household products (paint thinner, markers, felt pens, spray paints and glues, among others) and toluene is the main chemical compound present in most of them. Previous studies have shown that toluene produces memory impairment and environmental enrichment reverse these responses; however, there are limited research regarding the mechanisms involved in such effects. Therefore, in the first part of this study we evaluated the changes on glutamate in the hippocampus and prefrontal cortex (areas associated with memory impairments) in mice exposed to toluene. In the second part we evaluated the effect of environmental enrichment on glutamate concentrations in mice with history of toluene exposure. To fulfill both objectives young male mice were exposed to toluene during four weeks. In a group of animals the brains areas were dissected out and glutamate concentrations analyzed by HPLC. Another group of mice were exposed to toluene and afterwards they were housed either on environmental enrichment or on standard conditions. Evaluation of glutamate was also conducted after 4 weeks of housing treatment. Results showed that toluene did not significantly modify glutamate content in either of the areas evaluated. Similarly, environmental enrichment did not produced alterations on glutamate concentrations in both areas. Results may suggest that glutamate changes may not be associated with memory alterations after toluene exposure; likewise glutamate alterations may not be responsible for the reversal of memory detriments after environmental enrichment.

Disclosures: **N. Paez-Martinez:** None. **R. Solis-Guillen:** None. **S. Montes-Lopez:** None.

Poster

780. Translational Studies of Treatments for Addiction

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Topic: C.17. Drugs of Abuse and Addiction

Support: MRC Grant MR/M007006/1

Title: Retrieval-dependent changes in craving and alcohol-memory following reappraisal in high-risk drinkers: a model for reconsolidation-based cognitive therapy?

Authors: *S. K. KAMBOJ, T. HON, R. K. DAS;
Univ. Col. London, London, United Kingdom

Abstract: Introduction: Reconsolidation is implicated in the strengthening and modification of long-term memories. 'Reappraisal' is an emotion regulation procedure used in cognitive behavioural therapy, which aims to modify 'dysfunctional thoughts' so that their meaning is less threatening or more adaptive. Here we examine whether retrieval procedures designed to destabilise alcohol memories can alter accessibility of alcohol-related thoughts, craving, attentional bias and drinking behaviour. Methods: On Day 1 participants either retrieved alcohol-related memories using one of two retrieval procedures - Value Prediction-Error (n=15) or Omission Prediction-Error (n=16) - or did not retrieve alcohol memories (Control; n=16). After this, participants identified six dysfunctional alcohol-related thoughts, which related to their reasons for drinking excessively. They then generated alternative, more balanced thoughts (reappraisals) for each of the six unhelpful thoughts. Memory for these reappraisals and general access to alcohol related memories (alcohol fluency) was assessed at the end of Day 1 and again one week later (Day 8). Alcohol craving and drinking behaviour (over the previous 7 days) were also assessed on both days, and attentional bias (eye movements) on Day 8. Results: The Omission Prediction-Error group showed a reduction in fluency for positive alcohol-related words on Day 8, along with a reduced current desire to drink (purposefulness-craving). Conclusions: This preliminary study employs an emotion regulation strategy commonly used in cognitive therapy (reappraisal) in the context of memory retrieval procedures designed to cause memories to become unstable and susceptible to modification (reconsolidation). We found preliminary evidence that omitting an expected reward during retrieval (Omission Prediction-Error) prior to generating new, adaptive appraisals related to moderate drinking, resulted in reductions in accessibility of positive alcohol-related words. These findings have implications for the development of psychological treatments through the incorporation of behavioural neuroscience findings.

Disclosures: **S.K. Kamboj:** None. **T. Hon:** None. **R.K. Das:** None.

Poster

780. Translational Studies of Treatments for Addiction

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 780.08/J6

Topic: C.17. Drugs of Abuse and Addiction

Support: RCN Grant 213751

Title: Preclinical studies of a passive vaccine against heroin

Authors: ***I. BOGEN**, A. M. S. KVELLO, J. MØRLAND, J. M. ANDERSEN;
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Abstract: Passive immunization with monoclonal antibodies is currently being studied as an alternative treatment strategy for drug overdose and addiction. The aim of such antibody therapy is to sequester the active drug in the blood and thereby prevent the psychoactive substance from entering the brain and exert its effects. The acute effects of heroin are mainly caused by its first metabolite, 6-monoacetylmorphine (6-MAM), which is rapidly formed in the blood before crossing the blood-brain-barrier and binding to brain opioid receptors. In a recently published study, we reported that a monoclonal antibody specific to 6-MAM (anti 6-MAM mAb) reduces acute heroin-induced effects in mice (Bogen et al., 2014). The aim of the present study was to characterize the time course of the interference of the antibody with heroin effects and to assess μ-opioid receptor binding after heroin injection in mAb-treated animals and controls. Furthermore, we wanted to elucidate the efficacy of the antibody upon repeated heroin injections. Mice were pretreated with anti-6-MAM mAb (10 mg/kg) or saline, followed by one or several injections of heroin (2.5 μmol/kg). Immediately after the last heroin injection, the behavioral drug effect was assessed in a locomotor activity test, which may be used as a measure of the psychostimulatory effects of opioids. Blood and brain levels of opioids were quantified by LC-MSMS. A radioligand assay employing [3H]DAMGO was used to examine μ-opioid receptor binding *ex vivo*, comparing mAb treated animals and controls. The behavioral effects of heroin, measured as locomotor activity, were reduced by approximately 60% in mAb-treated animals compared to controls. The brain levels of 6-MAM were reduced by 27, 32 and 60% in mAb-treated animals when measured 5, 10 and 25 minutes after heroin administration, respectively. Furthermore, a single dose of anti-6-MAM mAb reduced the brain concentration of 6-MAM by approximately 60% even after daily repeated heroin injections for three consecutive days. We found a 36% increase in available μ-opioid receptors in the brains of mAb-treated mice

compared to controls, indicating decreased levels of opioids in these animals. The results from the current study confirm that anti-6-MAM mAb treatment reduces the acute behavioral effects of heroin by blocking the entry of 6-MAM to the brain. Moreover, our results indicate that anti-6-MAM mAb reduces heroin-induced effects even after repeated drug exposure.

Disclosures: I. Bogen: None. **A.M.S. Kvello:** None. **J. Mørland:** None. **J.M. Andersen:** None.

Poster

780. Translational Studies of Treatments for Addiction

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 780.09/J7

Topic: C.17. Drugs of Abuse and Addiction

Support: R01DA0033459

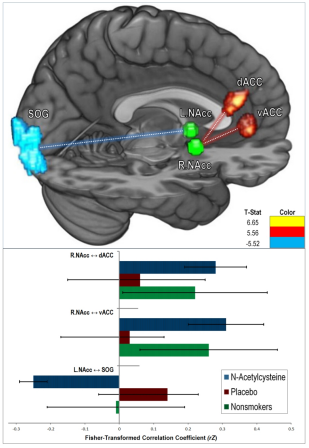
P50DA015369

Title: The effects of N-Acetylcysteine on corticostriatal resting-state functional connectivity mediate nicotine withdrawal symptoms and may help prevent relapse

Authors: *B. FROELIGER[1], P. A. MCCONNELL[2], P. W. KALIVAS[1], K. M. GRAY[1]; [1]Neurosciences, Med. Univ. of South Carolina, Charleston, SC; [2]Neurosci., Med. Univesity of South Carolina, Charleston, SC

Abstract: BACKGROUND: Chronic exposure to drugs of abuse disrupts corticostriatal glutamate transmission, which in turn meditates drug seeking. In animal models, N-acetylcysteine normalizes dysregulated frontostriatal glutamatergic neurotransmission and prevents reinstated drug seeking; however, the effects of N-Acetylcysteine on human corticostriatal circuitry function and preventing smoking relapse is unknown. METHODS: The present study examined the effects of N-Acetylcysteine on corticostriatal resting-state functional connectivity (rsFC), nicotine withdrawal symptoms and maintaining abstinence. Healthy adult smokers (N=16; mean (SD) age 36.5±11.9; cigs/day 15.8±6.1; yrs/smoking 15.7±8.9) were randomized to a double-blind course of 2400 mg N-Acetylcysteine (1200 mg b.i.d.) or placebo over the course of 3 ½ days of monetary-incentivized smoking abstinence. On each abstinent day, measures of mood and craving were collected digitally, and participants attended a lab visit in order to assess smoking (i.e., expired-air carbon monoxide [CO]). On day 4, participants underwent fMRI scanning. A demographically-matched nonsmoker control-group (N=16) was

scanned once for comparison. RESULTS: As compared to placebo (n=8), smokers in the N-Acetylcysteine group (n=8) maintained abstinence, reported less craving and higher positive affect (PA) (all p's <.01), and concomitantly exhibited stronger frontostriatal and weaker visuostriatal rsFC [p<.05; FWE]). Frontostriatal rsFC was negatively correlated with CO and fully mediated the relationship between craving and PA. Finally, no differences in rsFC or affect were found between the N-Acetylcysteine group and nonsmokers. CONCLUSIONS: Taken together, these findings suggest that N-Acetylcysteine may normalize dysregulated corticostriatal connectivity, help to restructure reward processing, and reduce vulnerability to relapse after quitting smoking.



Disclosures: **B. Froeliger:** None. **P.A. McConnell:** None. **P.W. Kalivas:** None. **K.M. Gray:** None.

Poster

780. Translational Studies of Treatments for Addiction

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Program#/Poster#: 780.10/J8

Topic: C.17. Drugs of Abuse and Addiction

Support: McGill University Health Center

Title: Effects of LSD on the dopaminergic neurons of Ventral Tegmental Area. An *in vivo* electrophysiological study

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Abstract: Background: The effects of the hallucinogen D-lysergic diethilamide (LSD) are described as a "mystical experiences", "sensory journeys", pseudo-hallucinations, affective changes, enhancement of past memories. It was firstly synthetized in 1938 by A. Hofmann, but its mechanism of action has not yet completely elucidated. It is well known that LSD interacts with the serotonin (5-HT) system binding to 5-HT1 and 5-HT2 receptors (Peroutka and Solomon, 1973), decreasing the activity of 5-HT neurons in the Dorsal Raphe Nucleus (DRN) (Trulson and Jacobs, 1979) and increasing the firing rate of cortical neurons in the somatosensory cortex in rats (Marek and Aghajanian, 1996). However, little is known of its potential interactions with the dopamine (DA) neurons of the Ventral Tegmental Area (VTA). In this study, we first evaluated the effects of LSD on DA neuron activity in the parabrachial nucleus of VTA, and second, we compared these effects to those produced on 5-HT neurons in the DRN. Third, we pretreated rats with p-chlorophenylalanine (PCPA), an inhibitor of 5-HT synthesis, to test whether the effects of LSD on DA neurons are mediated by the 5-HT system. Methods: Using *in vivo* electrophysiology, we studied the effects of cumulative doses of LSD (10-90 ug/kg, i.v.) on DRN 5-HT and VTA DA neurons in Sprague Dawley male adult rats. A second group of rats was pretreated with PCPA (350 mg/kg, i.p.) 48-h and 24-h before VTA DA recordings. Results: LSD induced a significant decrease of DRN 5-HT firing activity at the dose of 10 ug/kg, and switched off the firing at 20 ug/kg (n=6). These doses did not affect DA neuronal activity. At the dose of 60 ug/kg, LSD decreased DA firing activity (vehicle: 2.42 ± 0.95 Hz; LSD 60 ug/kg: 1.44 ± 0.61 Hz, n=6), while at 90 ug/kg it completely shut down VTA DA activity ($p<0.05$ versus vehicle, n=6). Notably, the injection of cumulative doses of the selective D2 antagonist haloperidol (0.05-15 mg/kg, i.v.) was able to reinstate the activity of DA neurons (1.53 ± 1.23 Hz, $p<0.05$, n=6). In PCPA-pretreated rats, LSD decreased the activity of VTA DA neurons similarly to non-treated rats (vehicle: 2.04 ± 0.64 Hz; LSD 60 ug/kg: 0.40 ± 0.29 Hz, $p< 0.05$, n=4), but in this case, haloperidol (0.05-0.25 mg/kg, i.v.) was not able to reinstate DA neuronal activity. Discussion: These results suggest that LSD modifies the DA system independently from the 5-HT system and D2 receptors. Furthermore, it confirms that the 5-HT system plays an inhibitory role on VTA DA neurons through the modulation of D2 receptor.

Disclosures: D. De gregorio: None. **L. Posa:** None. **S. Comai:** None. **F. Rossi:** None. **V. De novellis:** None. **S. Maione:** None. **G. Gobbi:** None.

Poster

780. Translational Studies of Treatments for Addiction

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Topic: C.17. Drugs of Abuse and Addiction

Support: National Natural Science Foundation of China No. 31170990

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Title: Cognitive behavioral therapy normalized abnormal neural circuits at resting state in Internet gaming disorder

Authors: *Y. YAO[1], J. ZHANG[1], C.-S. R. LI[3], L. LIU[2], L. WANG[1], B. LIU[1], S. MA[1], X. FANG[2];
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Abstract: Internet gaming disorder (IGD) has become a serious mental health issue worldwide. Developing effective interventions for IGD and evaluating the benefits of these interventions are of great significance. Evidence suggests that IGD is associated with altered brain structures and functions, thus investigating neurobiological abnormalities of IGD would advance our understanding of its underlying mechanism and provide information to develop more tailored interventions. Resting-state fMRI offers an effective way to measure intrinsic brain activities without the burden of specific tasks, and has been used as an objective measure to assess the effects of interventions in IGD. The aims of this study were to identify regional abnormalities and related altered neural circuits in IGD during resting-state, and how cognitive behavioral therapy (CBT) takes effect at circuits level. Forty-one young adults with IGD and 19 age- and sex-matched healthy controls (HCs) were recruited, and their resting-state fMRI data were collected. Twenty-three IGD subjects (IGDs) participated in a group CBT once a week lasting for six weeks, and were scanned before and after the intervention. The remaining 18 IGDs did not receive an intervention, but were similarly scanned at the same time points. We firstly compared amplitude of low frequency fluctuation (ALFF) between 41 IGDs and 19 HCs before intervention, and found that IGDs showed decreased ALFF in the posterior cingulate cortex (PCC) and frontal pole. We further examined alteration in resting-state functional connectivity (rsFC) of these two regions using seed-based correlation analysis, and found that IGDs exhibited increased rsFC between PCC and dorsolateral prefrontal cortex. Finally, we examined the effects of CBT on rsFC in IGD. Compared with IGDs who did not receive intervention, IGDs receiving CBT demonstrated significantly reduced interactions between PCC and precentral gyrus, and between frontal pole and hippocampus/parahippocampus. These findings suggest that IGD is associated with abnormal spontaneous activity and maladaptive interactions between regions within default mode network (DMN) and executive cognitive network (ECN). Furthermore, CBT

may exert its effect by reducing the interactions between ECN and DMN, and between regions in ECN and components in reward system.

Disclosures: **Y. Yao:** None. **J. Zhang:** None. **C.R. Li:** None. **L. Liu:** None. **L. Wang:** None. **B. Liu:** None. **S. Ma:** None. **X. Fang:** None.

Poster

780. Translational Studies of Treatments for Addiction

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NCRR 5G12RR003060-26

NIMHHD 8G12MD7603-27

NINDS R25NS076414

NIDA R25DA030310

Title: Hormone dependent efficacy of taurine as treatment for cocaine drug use: a study of reward

Authors: K. URIBE[1], S. PEREZ[2], U. AKPARA[3], D. WOO[3], S. SINGH[3], M. EVELYN[3], K. CHAUHAN[3], S. AYO[3], F. JACQUES[3], M.-R. MURITALA[3], S. SOYEMI[3], D. PETERS[1], A. COLE[3], P. DUVALSAINT[3], A. ELZANIE[3], D. HARRIS[3], S. MARACHERIL[3], *K. Y. SALAS-RAMIREZ[3];
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Abstract: Cocaine is a commonly abused psychostimulant that causes alterations to the mesocorticolimbic circuitry and addiction-related behaviors. Females have been shown to be more vulnerable to the effects of cocaine than males. Taurine is an essential amino acid that displays several neuropsychopharmacological roles such as neuromodulator, neurotrophic, and osmomodulatory roles. Previous data from our laboratory shows that males and females form a preference to cocaine but pre-treatment of taurine attenuates cocaine preference to non-significant levels. The objective of the present study is to determine if exposure to taurine will

reduce cocaine preference in gonadectomized (GDX) male and female subjects and elucidate whether gonadal hormones affect taurine's efficacy and potential for cocaine treatment. Males and females were run in two cohorts (n = 36; n=9/treatment group). The cohorts were divided into four groups. The first group are injected with taurine pretreatment and taurine+cocaine coadministration treatment (pre-tau/coc+tau), the second group is exposed to taurine pretreatment and cocaine+saline coadministration treatment (pre-tau/coc+sal), the third group also received the taurine pretreatment and taurine+saline coadministration treatment (pre-tau/tau+sal), and the fourth group is saline-pretreatment and cocaine+saline coadministration treatment (pre-sal/coc+sal). The rats are pretreated with taurine (100mg/kg) or saline (intraperitoneal) for two weeks before undergoing a ten-day conditioned place preference (CPP) behavioral paradigm where a context will be paired with a drug stimulus (taurine or cocaine). GDX males acquired cocaine preference, and taurine inhibited cocaine reward under all conditions. GDX did not acquire a preference to taurine. Although GDX-females do not form a cocaine-preference, interestingly, GDX-females did acquire a preference to the taurine-paired chamber ($p<0.0064$). These results suggest taurine is potentially a good candidate for cocaine addiction but further research will need to elucidate how hormones modulates taurine's efficacy since GDX-females seem to be sensitive to the effects of taurine. Cocaine-induced behaviors can persist for years even after abstinence and the best form of treatment is still being elucidated.

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Poster

780. Translational Studies of Treatments for Addiction

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Program#/Poster#: 780.13/J11

Topic: C.17. Drugs of Abuse and Addiction

Support: R01DA019946

R01NS073884

R21MH073624

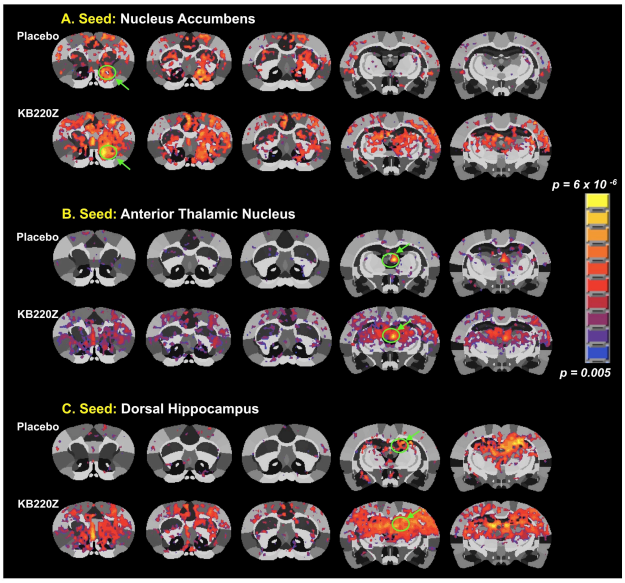
R01HD70888

P01HD075750

Title: Putative dopamine agonist KB220Z enhances resting state brain reward circuit functional connectivity

Authors: K. BLUM[1], *M. FEBO[1], R. D. BADGAIYAN[2], P. D. PEREZ[1], L. M. COLON-PEREZ[1], P. K. THANOS[3], C. F. FERRIS[4], P. KULKARNI[4], J. GIORDANO[5], M. S. GOLD[1]; [1]Psychiatry Dept., Univ. of Florida, Gainesville, FL; [2]Psychiatry, Univ. of Minnesota, Minneapolis, MN; [3]Psychology, SUNY Stonybrook, Stony Brook, NY; [4]Psychology, Northeastern Univ., Boston, MA; [5]Dept. of Holistic Med., Natl. Inst. of Holistic Addiction Studies, North Miami Beach, FL

Abstract: Dopaminergic reward dysfunction in addictive behaviors is well supported in the literature. Several lines of evidence support the notion that alterations in synchronous neural activity between brain regions subserving reward and various cognitive functions, may significantly contribute to substance-related disorders. An electronic rat atlas was used to evaluate resting state functional connectivity in brain reward circuitry. This study presents the first strong evidence showing that a putative dopamine agonist nutraceutical (KB220Z) significantly activates, above placebo, seed regions of interest including the left nucleus accumbens, cingulate gyrus, anterior thalamic nuclei, hippocampus, pre-limbic and infra-limbic loci. This response induced by KB220Z demonstrates significant functional connectivity, increased brain volume recruitment and enhanced dopaminergic functionality across the brain reward circuitry. This robust yet selective response implies clinical relevance.



Disclosures: K. Blum: None. **M. Febo:** None. **R.D. Badgaiyan:** None. **P.D. Perez:** None. **L.M. Colon-Perez:** None. **P.K. Thanos:** None. **C.F. Ferris:** None. **P. Kulkarni:** None. **J. Giordano:** None. **M.S. Gold:** None.

Poster

780. Translational Studies of Treatments for Addiction

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Program#/Poster#: 780.14/J12

Topic: C.17. Drugs of Abuse and Addiction

Support: ISC III Grant FIS PI10/00440

Title: Food craving in morbid obesity: influence on biological variables and bariatric surgery outcomes

Authors: *J. R. MUÑOZ-RODRÍGUEZ[1], F. POLO[1], L. BEATO[1], J. MARTÍN[1], C. GONZÁLEZ-MARTÍN[2], E. SEGURA[1], G. CASAS[1], A. LEÓN[1], E. SALAS[1], L. F. ALGUACIL[2];
[1]Translational Res. Unit, Univ. Gen. Hosp. of Ciudad Real, Ciudad Real, Spain; [2]CEU San Pablo Univ., Boadilla, Madrid, Spain

Abstract: It has been recently estimated that 20% of obese subjects are suffering from food addiction. These subjects may represent a specific endophehotype of obesity from both diagnostic and prognostic points of view. To further define this endophenotype, we have comparatively studied a broad set of biomarkers in morbid obese patients with high and low food cravings. Besides, we have compared the evolution of these biomarkers in both groups one year after bariatric surgery treatment. 23 morbid obese patients (BMI>40; 16 females and 7 males aged 44±3 years) and a group of normoweight controls (18,5>BMI<25) matched by sex and age were recruited. Patients were administered with the Spanish version of the State and Trait Food Cravings Questionnaire, trait scale, in order for them to be subdivided into two groups according to their craving scores: high food craving (HFC, with "loss of control" dimension score ≥15, n=13) and low food craving (LFC, with "loss of control" dimension score <15, n=10). Serum samples were obtained from all subjects to quantify clinical routine parameters and biomarkers of renal and liver function, metabolism and inflammation, as well as hormones and neuropeptides of interest. Quantifications were repeated one year after bariatric surgery (gastric bypass). Routine parameters were determined by conventional clinical tests while hormones and neuropeptides were determined by ELISA. Statistics was performed in SPSS v19.0 using two-way repeated-measures ANOVA with "craving" (LFC, HFC) and "treatment" (pre-surgery, post-surgery) as independent variables and Bonferroni post hoc for multiple comparisons. Data analysis revealed that carbohydrate metabolism was differentially affected in HFC and LFC subjects, the latter exhibiting higher values of HOMA-1%β and 2%β along the study. Bariatric surgery was effective to decrease body mass indexes and correct many biochemical and

metabolic alterations to a similar extent in both HFC and LFC patients; however, the magnitude of change in total cholesterol, LDL, HOMA-2%β, Mg and Fe only achieved statistical significance in HFC subjects. By contrast, patients of the LFC group were the only to exhibit a partial recovery of ghrelin and vitamin D1 levels post-surgery, and were resistant to BDNF downregulation below control values. These results together with complementary data from proteomics and metabolomics performed in our laboratory strongly suggest that morbid obese patients have different metabolic profiles and different response to bariatric surgery depending on their food cravings, thus supporting the importance of further progressing in the definition of an "addictive" endophenotype of obesity.

Disclosures: **J.R. Muñoz-Rodríguez:** None. **F. Polo:** None. **L. Beato:** None. **J. Martín:** None. **C. González-Martín:** None. **E. Segura:** None. **G. Casas:** None. **A. León:** None. **E. Salas:** None. **L.F. Alguacil:** None.

Poster

780. Translational Studies of Treatments for Addiction

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Program#/Poster#: 780.15/J13

Topic: C.17. Drugs of Abuse and Addiction

Support: NIH grant AT006899

NIH grant DA013429

Title: Metabolism of L-tetrahydropalmatine (L-THP) in rats and *in vitro* effects of its major metabolites on dopamine receptors

Authors: P. HUANG[1], I. ABDALLAH[2], J. LIU[3], W. HEDRICH[2], D. Y. LEE[3], H. HASSAN[2], *L.-Y. LIU-CHEN[1];
[1]Ctr. for Substance Abuse Res., Temple Univ. Sch. Med., Philadelphia, PA; [2]Dept. of Pharmaceut. Sci., Univ. of Maryland Sch. of Pharm., Baltimore, MD; [3]Bio-Organic and Natural Products Lab., McLean Hospital, Harvard Med. Sch., Belmont, MA

Abstract: L-THP is currently in a clinical trial for treatment of cocaine addiction in the US. Here we reported its metabolism in rats and the *in vitro* pharmacology of its major metabolites. Following i.p. injection, L-THP was immediately absorbed into the blood and appeared in the brain. Metabolism of L-THP occurred rapidly with L-corydalmine (L-CD) and L-corypalmine (L-CP) as the two major metabolites, which peaked in the plasma at 15 min after i.p. injection.

Following 30 mg/kg i.p. injection of L-THP, the plasma and brain levels were in the order of L-THP > L-CD > L-CP at all time points examined (from 15 min to 24 h). After 10 mg/kg i.p. injection, the plasma and brain levels were in the same order at two time points examined (30 min and 4 h). L-THP appeared to have first-order metabolism with a $T_{1/2}$ of about 2 h. The receptor binding and functional properties of L-CD, L-CP and L-THP on dopamine receptors were characterized using cell lines stably expressing each of the five human dopamine receptors (DR). [^{3}H]SCH23390 binding and stimulation of adenylyl cyclase were used to examine the effects on D1R or D5R, and [^{3}H]N-methyl-spiperone binding and [^{35}S]GTPγS binding assays were for D2R, D3R or D4R. L-CD, L-CP and L-THP showed similar affinity for D1R (K_i, 107-199 nM) and for D5R (K_i, 242-313 nM). The K_i values of L-CP to D2R and D3R were 42.4 and 262 nM, respectively, and of L-CD to D2R was 533 nM. The following interactions had low affinity (K_i >1 μM): L-THP with D2R and D3R; L-CD with D3R; L-THP, L-CD and L-CP with D4R. For D1R and D5R, compared with dopamine, both L-CD and L-CP were partial agonists, with lower efficacies for D5R. For D2R and D3R, neither activated the receptors and exhibited antagonist activities. At the D2 receptor, L-CP and L-CD at 1 μM shifted the dose-response curve of DA to the right and increased the EC_{50} value of DA by 15- and 5.8- fold, respectively. L-CP also reduced the E_{max} value of DA significantly. At the D3 receptor, L-CP and L-CD at 1 μM shifted the dose-response curve of DA to the right and increased the EC_{50} value of DA by 7.9- and 6.2-fold, respectively without changing the E_{max} value of DA. Thus, both L-CD and L-CP are D1R and D5R partial agonists and D2R and D3R antagonists, with lower potencies at D2R and D3R. The effects of L-THP on DR-mediated signaling are currently under investigation.

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Poster

780. Translational Studies of Treatments for Addiction

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Topic: C.17. Drugs of Abuse and Addiction

Support: AA020919

DA035958

Title: Dopamine D2 receptors as peripheral biomarkers for brain dopamine levels and as targets for modulating brain dopamine

Authors: *S. C. STEFFENSEN[1], E. Y. JANG[1], H. J. PARK[1], B. GARCIA[1], G. F. BURTON[1], S. H. BURNETT[1], J. G. LEE[2], C. H. YANG[2];
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Abstract: Dopamine (DA) D2 autoreceptor (D2R) expression in the midbrain and striatum is a well-known biomarker for brain DA levels. Markers of D2R expression are not only detectable in the brain, but are also expressed in peripheral tissues, including blood, where DA appears to play a pivotal role in mediating communication between the nervous and immune systems. The aim of this study was to evaluate the expression of D2Rs on WBCs following exposure to DA and D2R agonists/antagonists, and to correlate expression with DA release in the nucleus accumbens (NAc) of the striatum, as well as locomotor and self-administration behavior. Using fluorescent flow cytometry and immunohistochemistry, D2Rs were expressed in WBCs in mice, rats and humans. However, their expression in rats was mostly limited to activated monocytes, which was the focus of this study. D2R expression in monocytes decreased at 2 hrs by 50% following administration of the centrally-acting D2R antagonist eticlopride (1.0 mg/kg IV) and increased at 2 hrs by 75% following administration of the centrally-acting D2R agonist quinpirole (0.1 mg/kg IV). However, D2R expression in the NAc exhibited opposite effects at 2 hrs to those in the blood. Concomitantly, using fast-scan cyclic voltammetry (FSCV), phasic DA release in the NAc was markedly enhanced 320% by eticlopride and reduced 76% by quinpirole with an onset in minutes and duration of 2 hrs. Surprisingly, intravenous administration of DA (0.1-3.0 mg/kg) enhanced DA release 2000% in the NAc with a lag of 20 min. This marked increase in DA release was not due to the blood pressure enhancing effects of DA via alpha adrenergic receptors. Intravenous DA resulted in complex behavioral effects depending upon dose, which included freezing at higher doses and activation at lower doses. Preliminary immunohistochemical studies have revealed expression of D2Rs in brain microglia after IV DA injection. These findings suggest that DAergic drugs not only yield rapid changes in brain D2 receptor expression, but elicit changes in peripheral D2 receptor expression that appear to be inversely correlated. In addition, activation of peripheral D2Rs may be a potential therapeutic target to raise brain DA levels. These results have significant clinical potential as changes in peripheral D2 receptor expression could be monitored as biomarkers of brain DA and used for the treatment of addiction as well as other diseases involving DA including Parkinson's disease.

Disclosures: S.C. Steffensen: None. **E.Y. Jang:** None. **H.J. Park:** None. **B. Garcia:** None. **G.F. Burton:** None. **S.H. Burnett:** None. **J.G. Lee:** None. **C.H. Yang:** None.

Poster

780. Translational Studies of Treatments for Addiction

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 780.17/J15

Topic: C.17. Drugs of Abuse and Addiction

Title: Prefrontal cortical correlates of inhibitory control in patients with alcohol use disorders

Authors: *J. D. HARRIS[1], A. HUHN[1], E. DENEKE[2], H. AYAZ[3], R. MEYER[1], S. BUNCE[1]; [1]Psychiatry, Pennsylvania State Univ., Hershey, PA; [2]Res., Caron Treatment Centers, Wernersville, PA; [3]Biomed. Engin., Drexel Univ., Philadelpia, PA

Abstract: Alcohol use disorders have devastating effects to individuals' well-being and to public health at large. One key feature of alcohol use disorders is loss of control, which is related to impulsivity and deficits inhibitory control. Recent neuroimaging studies suggest that deficits in inhibitory control and related executive functions are mediated by dysfunction of the prefrontal cortex (PFC). Prefrontal cortical dysregulation is also hypothesized to mediate severity of alcohol dependence and increase relapse vulnerability following discharge from residential treatment. This study employs clinically applicable neuroimaging technology, functional near-infrared spectroscopy (fNIRS), to examine PFC function in patients with alcohol use disorders while performing a neuroimaging adaptation of the word-color Stroop paradigm. Incongruent minus neutral conditions were selected for the contrast of interest. Stimuli were presented a in block design, with 300ms stimulus presentation and 1300ms interstimulus interval. A subjective measure of inhibitory control was assessed using the Barratt Impulsivity Scale (BIS-11). Patients' task-related PFC activity over right inferior frontal gyrus (rIFG) correlated with BIS scores ($r(35) = 0.60$, $p = 0.001$). Of note, this relationship was found for patients, but not control participants ($r(14) = -0.15$, $p = 0.61$). Importantly, rIFG has been demonstrated in tasks related to inhibition. These data demonstrates the relationship between self-reported impulsivity, and underlying prefrontal cortical activity in patients with alcohol use disorders. Furthermore, this investigation demonstrates a cost-effective, objective brain based biomarker of impulsivity that may provide relevant data to help improve alcoholism treatment efficacy. The ongoing study is evaluating the utility of these data in the prediction of treatment outcome.

Disclosures: J.D. Harris: None. **A. Huhn:** None. **E. Deneke:** None. **H. Ayaz:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ownership Interest. **R. Meyer:** None. **S. Bunce:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ownership Interest.

Poster

780. Translational Studies of Treatments for Addiction

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 780.18/J16

Topic: C.17. Drugs of Abuse and Addiction

Support: NIDA-IRP, NIH/DHHS

Title: Reinforcing and neurochemical effects differentiate modafinil from methylphenidate in their interactions with cocaine

Authors: *G. TANDA[1], M. MEREU[1], T. HIRANITA[2], L. CHEN[1], J. LOPEZ[1], M. COGGIANO[1], J. QUARTERMAN[1], A. H. NEWMAN[3,1], J. KATZ[2];
[1]Medication Develop. Program, NIDA, Baltimore, MD; [2]Psychobiology Section, Natl. Inst. on Drug Abuse, Baltimore, MD; [3]Medicinal Chem. Section, Natl. institute on Drug Abuse, Baltimore, MD

Abstract: Modafinil (MOD) and methylphenidate are FDA-approved as a wakefulness-promoting agent, or for attention deficit disorder, respectively. They share with cocaine inhibition of dopamine (DA) reuptake by blockade of the DA-transporter, and have been tested in clinical studies as medications to treat cocaine-dependence. Non-medical use of MOD and methylphenidate as "smart drugs," in order to increase cognitive performance, especially by students, has been described. This population is also at risk for abuse of illicit stimulants, like cocaine. Interactions of MOD and cocaine have not yet been fully described, and information about the potential adverse effects of MOD in combination with an abused psychostimulant like cocaine is of public health importance. In the present study MOD (0.1-10 mg/kg iv) failed to maintain self-administration behavior in rats, whereas methylphenidate self-administration was maintained at doses equal to those for cocaine self-administration (0.1-1 mg/kg iv). However, pretreatments with MOD (10-32 mg/kg ip) or methylphenidate (1-10 mg/kg ip) potentiated cocaine self-administration, shifting the dose-effect curves to the left. Cocaine, at self-administered doses also produced dose-related stimulation of DA in the nucleus accumbens shell, a brain area involved in the reinforcing effects of drugs. Methylphenidate enhanced this stimulation whereas MOD was without significant effects. In summary, MOD has a unique stimulant profile compared to cocaine and methylphenidate. The results suggest MOD may enhance cocaine-induced reinforcing effects. However, there are no clinical reports of abuse of modafinil alone or in combination with psychostimulants; thus, it remains to be seen if the recreational use of "smart drugs" such as MOD will lead to the abuse of illicit substances. Recent clinical studies report positive therapeutic outcomes of MOD treatment in cocaine addicted subjects. The results herein support that at the very least MOD may decrease cocaine consumption, if not entirely achieve abstinence. In the absence of any approved medication for this patient population, it seems that a medication that appears to have no addictive liability on its own, but could reduce cocaine use would be of interest.

Disclosures: **G. Tanda:** None. **M. Mereu:** None. **T. Hiranita:** None. **L. Chen:** None. **J. Lopez:** None. **M. Coggiano:** None. **J. Quarterman:** None. **A.H. Newman:** None. **J. Katz:** None.

Poster

781. Hedonia, Feeding, and Addictive Drugs

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 781.01/J17

Topic: C.17. Drugs of Abuse and Addiction

Support: NSERC

Title: Is high fructose corn syrup as addictive as oxycodone? A study of dual intravenous and intraoral self-administration, extinction and reinstatement in rats

Authors: M. MINHAS, *F. LERI;
Psychology, Univ. Guelph, Guelph, ON, Canada

Abstract: Introduction: It is reported that highly palatable food can engender “addictive-like” patterns of consumption. Furthermore, there is substantial evidence in animals that palatable food activates brain reward centers in ways that closely resemble the action of drugs of abuse. These similarities suggest that "addiction" can develop to food. The current study investigated the hypothesis that sugar can be addictive as drugs of abuse by studying the self-administration (SA) of sugar and drugs in the same animals. Methods: Male, Sprague-Dawley rats were implanted with both intra-oral (IO) and intravenous (IV) cannulas and allowed to self-administer IO infusions of high fructose corn syrup (HFCS; 8, 25, 50%) and IV infusions of oxycodone (0.05, 0.1, and 0.2 mg/kg/inf) of 16 alternating days for 3 hrs/day. After a 4-day abstinence period, animals were tested in extinction conditions by presenting simultaneously both HFCS- and oxycodone-paired levers in the absence of the reinforcers. Extinction was followed by tests of priming-induced reinstatement. Results: Preliminary findings indicate that the pattern of SA for HFCS (50%) and oxycodone (0.1 mg/kg/inf) was similar either in the presence, or in the absence, of the reinforcers. Experimenter-administered injections of HFCS (50%; IO) or oxycodone (0.1 mg/kg; IV) reinstated responding that was specific to the levers previously associated with their self-administration. Conclusions: These findings indicate that high fructose corn syrup and oxycodone engender similar patterns of consumption and seeking in the same animal. Importantly, however, priming with one reinforcer does not induce seeking of the other. Funded by NSERC

Disclosures: **M. Minhas:** None. **F. Leri:** None.

Poster

781. Hedonia, Feeding, and Addictive Drugs

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 781.02/J18

Topic: C.17. Drugs of Abuse and Addiction

Support: Ontario Brain Institute

Title: Effect of bupropion and naltrexone on hedonic responses in laboratory rats

Authors: ***A. LEVY**[1], S. DANIELS[2], A. FLYNN[2], R. HUDSON[2], T. HORMAN[2], A. CHISHOLM[2], F. LERI[2];
[1]Psychology, [2]Univ. of Guelph, Guelph, ON, Canada

Abstract: Introduction: One defining feature of anhedonia is impaired reactivity to rewarding stimuli. We have been investigating two sub-processes of reward reactivity: set-point and primed-seeking. In this study, we attempted a pharmacological validation of these constructs by administering a bupropion (BUP; monoamine reuptake inhibitor) and naltrexone (NTX; opioid antagonist) alone, or in combination as employed to alleviate symptoms of depression in obese individuals. Methods and results: In animals trained to self-administer intraoral infusions of sugar in operant chambers on fixed ratio 1 schedules of reinforcement (measure of set-point seeking), acute or chronic administration of BUP+NTX reduced responding. Both acute and chronic NTX alone reduced sugar self-administration while BUP alone had no effect compared to vehicle. On a progressive ratio schedule (measure of primed-seeking), acute BUP+NTX and BUP alone enhanced sugar self-administration compared to vehicle and NTX alone. Similar effects were observed following chronic administration. In animals self-administering sugar from a sipper tube in home cages, chronic administration of combination BUP+NTX reduced both sugar and food intake. Alone, NTX also reduced sugar consumption without altering food intake; however, BUP did not affect either food or sugar consumption. Conclusions: These findings suggest that set-point and primed seeking can be pharmacologically dissociated. The former is primarily dependent on reward “satiety” and is enhanced by anorexic drugs like BUP and NTX. The latter is primarily dependent on reward “anticipation”, and is enhanced by monoamine activation, but only after acute administration. In combination, BUP and NTX act synergistically to increase reward satiety and primed-seeking.

Disclosures: **A. Levy:** None. **S. Daniels:** None. **A. Flynn:** None. **R. Hudson:** None. **T. Horman:** None. **A. Chisholm:** None. **F. Leri:** None.

Poster

781. Hedonia, Feeding, and Addictive Drugs

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 781.03/J19

Topic: C.17. Drugs of Abuse and Addiction

Support: The Ontario Brain Institute

Title: Exploring the anhedonic component of naltrexone precipitated high fructose corn syrup withdrawal

Authors: *S. DANIELS, P. MARSHALL, F. LERI;
Univ. of Guelph, Guelph, ON, Canada

Abstract: The affective component of withdrawal is a core feature of addiction. Negative emotional states last long after substance use has ceased, leaving individuals vulnerable to relapse even when physical symptoms have subsided. It has been suggested that withdrawal from sugars produces a set of somatic symptoms resembling those of opiate drugs. However, whether the affective component of withdrawal relates to consumption of sugars remains unknown. Therefore, the current study determined whether naltrexone (NTX) could precipitates conditioned place avoidance (CPA) in laboratory rats receiving acute or chronic pre-exposure to a HFCS solution. To interpret the findings, the same experiments were repeated in rats pre-exposed to acute or chronic heroin. In different experiments, animals received: intragastric acute administration of high fructose corn syrup (HFCS; 0.5, 1 or 2 g/kg); drank 0% or 50% solutions of HFCS in their home cages for 22 days (food restricted and non-food restricted); received acute subcutaneous (SC) injections 2 mg/kg heroin; or were implanted (SC) with osmotic mini-pumps releasing 3.5 mg/kg/day heroin. Following pre-treatments, animals were tested on CPA induced by NTX (1 or 3 mg/kg, SC). HFCS pre-exposure did not significantly amplify CPA induced by NTX. Food restricted rats with increased HFCS consumption demonstrated NTX-induced CPA not seen in animals given 0% HFCS, yet no significant interaction was observed. NTX-induced CPA with acute infusions of HFCS at higher but not lower doses, yet effects were not significantly different from 0% HFCS. Animals given acute and chronic heroin pre-exposure showed a NTX-induced CPA that was significantly different from control animals. These results fail to support the hypothesis that an opioid antagonist can precipitate similar affective withdrawal states following pre-exposure to sugars and opiates.

Disclosures: **S. Daniels:** None. **P. Marshall:** None. **F. Leri:** None.

Poster

781. Hedonia, Feeding, and Addictive Drugs

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 781.04/J20

Topic: C.17. Drugs of Abuse and Addiction

Support: OBI Grant 63251

Title: The role of the central endocannabinoid system in anhedonia

Authors: *D. HAYNES, C. L. LIMEBEER, L. A. PARKER, F. LERI;
Psychology, The Univ. of Guelph, Guelph, ON, Canada

Abstract: Recent evidence has implicated the endocannabinoid system, particularly the centrally-abundant cannabinoid receptor type 1 (CB1 receptor), in hedonic processing as well as anhedonia, the inability to experience pleasure. CB1 inverse agonists in particular have been shown to elicit typical anhedonic pathology in both humans and animals when administered chronically, with studies of the latter showing suppression of palatable food consumption, hedonic taste response to highly palatable flavours, and operant responding for a palatable food reward, indicative of an anhedonic state. However, the majority of these findings originate from studies employing systemic administration, which has been shown to elicit nausea alongside anhedonia. Recent research indicates that direct administration to the lateral ventricles eliminates this nausea component while appearing to preserve the anhedonic component. The present study sought to determine whether chronic intracerebroventricular (ICV) administration of CB1 inverse agonist AM251 is capable of inducing a persistent anhedonic state and to examine the role of the central CB1 receptor in anhedonia. Naïve male Sprague-Dawley rats received direct, chronic infusion of AM251 or vehicle via subcutaneous osmotic minipump into the right lateral ventricle, or underwent sham surgery. Hedonic capacity was assessed via changes in ad libitum consumption of a sweet, highly-palatable solution (high-fructose corn syrup; HFCS), as well as hedonic taste response to an intraoral infusion of HFCS. Preliminary results revealed a trend indicating persistent suppression of HFCS consumption by ICV AM251, consistent with an anhedonic state. However, there did not appear to be any significant difference in taste reactivity to HFCS. Final results will be presented at the meeting.

Disclosures: **D. Haynes:** None. **C.L. Limebeer:** None. **L.A. Parker:** None. **F. Leri:** None.

Poster

781. Hedonia, Feeding, and Addictive Drugs

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Program#/Poster#: 781.05/J21

Topic: C.17. Drugs of Abuse and Addiction

Support: OBI - Ontario Brain Institute

CIHR - Canadian Institutes of Health Research

NSERC - Natural Sciences and Engineering Research Council of Canada

Title: The influence of polyunsaturated fat diets on brain membrane lipid composition, leptin responsiveness and predisposition to anhedonia

Authors: *M. FERNANDES, D. MUTCH, F. LERI;
Univ. of Guelph, Guelph, ON, Canada

Abstract: Introduction: Dietary fat intake and the subsequent changes in brain membrane fatty acid composition have been implicated in the development of and susceptibility to some mental illnesses. Consistent with that, polyunsaturated fatty acids (PUFAs) differently affect depression-related behaviors: Omega-3 (n-3) PUFAs are known to reduce depression, while elevated intake of foods rich in Omega-6 (n-6) PUFAs are associated with an increase in the incidence of depressive disorders. Notably, it is well known that dietary lipid composition affects sensitivity to peripheral hormones, including leptin - PUFAs consumption promotes peripheral, but not central, leptin resistance. In addition, the localization of the leptin receptor in limbic structures implicated in the control of mood and emotion, such as the hippocampus, cortex and amygdala, suggest a potential role for leptin in hedonic behaviors. Providing further connection between mood disorders and adiposity signals, a number of reports suggested that leptin has antidepressant-like properties. Therefore, we hypothesize that long-term intake of n-3 or n-6 PUFA-rich diets will differentially modulate anhedonic behaviors by altering brain membrane lipid composition and leptin responsiveness in Sprague-Dawley rats. Methods: Sprague-Dawley rats fed an omega-3 or omega-6 PUFA-diet for 4 weeks will be euthanized and brain tissue will be collected for brain membrane lipid composition analyses (gas chromatography), endocannabinoid-system metabolites (liquid chromatography-mass spectrometry) and assessment of leptin signaling in the brain (western blotting). Epididymal and inguinal fat pads were removed from the above-mentioned rats and used for adipose tissue organ culture (ATOC), a well characterized technique that has been used to determine changes in adipose tissue metabolism and gene expression. A different cohort of rats maintained in the same dietary

condition was tested for anhedonic-like behaviors. Conclusion: These studies will provide valuable and novel information on the involvement of peripheral signals, such as fatty acids and leptin, in the pathophysiology of anhedonia and associated conditions, such as depression, obesity and substance dependence.

Disclosures: **M. Fernandes:** None. **D. Mutch:** None. **F. Leri:** None.

Poster

781. Hedonia, Feeding, and Addictive Drugs

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 781.06/J22

Topic: C.17. Drugs of Abuse and Addiction

Support: NSERC

CRC

FRSQ

Title: What about the cue? Modulation of cue value in the augmentation of heroin seeking in chronically food restricted rats

Authors: ***F. SEDKI**[1], L. MAYERS[2], P. MARTONE[2], U. SHALEV[2];
[1]CSBN, [2]Concordia Univ., Montreal, QC, Canada

Abstract: Disruptions in energy balance can largely affect motivated behaviours. For example, dietary restriction can increase drug intake in humans and rodents alike. Recently, we reported augmented heroin seeking in chronically food restricted rats under withdrawal. However, the underlying motivational mechanisms that drive this effect remain unclear. It is possible that exposure to caloric restriction may enhance the incentive salience attributed to drug-associated cues, and in turn augment drug seeking. Thus, we investigated the effect of food restriction on heroin seeking under a progressive ratio schedule of reinforcement, and on the acquisition of a new operant response reinforced solely by heroin-associated cues. Male Long-Evans rats were trained to self-administer heroin, by way of lever responses, for 10 days in operant conditioning chambers. Heroin infusions were associated with a complex light/tone stimulus. Next, rats were moved to the animal colony and maintained on free access to food (Sated group) or subjected to 14 days of mild chronic food restriction (FDR group), which sustained their body weight at 90% of their baseline weight. On day 14, rats underwent a 3 h heroin-seeking test under extinction conditions in the operant conditioning chambers. Exp.1: Rats were exposed to a progressive ratio

schedule of reinforcement driven solely by the heroin-associated cue. Exp. 2: The value of the cue was assessed by training the rats on a novel nose-poke response reinforced solely by the heroin-associated cues. Rats were tested across 3 sessions separated by 5 days each. Rats in the Sated and FDR groups demonstrated a robust increase in lever responding during the progressive ratio procedure, however no differences were observed between groups (Exp. 1). When exposed to a novel nose-poke procedure, rats in the FDR group acquired the novel behaviour at a greater rate compared to the Sated group. Furthermore, the enhanced acquisition of this novel behaviour persisted across multiple trials. Thus, while we did not observe differences in a progressive ratio task driven by cues alone, the value of a previously heroin-associated cue is enhanced by food restriction, and this augmented value is sustained across multiple tests.

Disclosures: F. Sedki: None. **L. Mayers:** None. **P. Martone:** None. **U. Shalev:** None.

Poster

781. Hedonia, Feeding, and Addictive Drugs

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 781.07/J23

Topic: C.17. Drugs of Abuse and Addiction

Support: NSERC

CRC

FRSQ

Title: Blocking D1 receptors in the nucleus accumbens core but not shell decreases the augmentation of heroin seeking induced by chronic food restriction in the rat

Authors: *T. M. D'CUNHA, D. RIZZO, G. MOURRA, M. RUSSO, F. SEDKI, U. SHALEV; Psychology, Concordia Univ., Montreal, QC, Canada

Abstract: Dieting or chronic food restriction and drug craving during abstinence increases the risk to relapse in human addicts. Recently, we demonstrated that chronic food restriction during withdrawal augments heroin seeking in rats with a history of heroin self-administration. Moreover, this prolonged restriction increases extracellular dopamine levels in the nucleus accumbens (NAc) core and shell during a heroin-seeking test. Thus, we expect that blocking dopamine transmission in the NAc core or shell will reverse the augmentation of heroin seeking induced by chronic food restriction. Here, rats were trained to self-administer heroin for 10 days in operant conditioning chambers. Next, rats were moved to the animal colony for 14 days of

withdrawal during which they were given either unrestricted access to food or subjected to a mild chronic food restriction to reduce their body weight to approximately 90% of their baseline weight. On day 14 of withdrawal rats were returned to the operant conditioning chambers for a 3 h heroin-seeking test under extinction conditions. Rats were administered the selective dopamine D1 receptor antagonist SCH 39166 into the NAc shell (0.0, 12.5, 25.0, 50.0 ng/side) or the NAc core (0.0, 12.5, 25.0 ng/side) prior to testing. As expected, food restriction significantly augmented heroin seeking compared to the sated rats. SCH 39166 administration (25.0 & 50.0 ng/side) into the NAc shell decreased cue-induced heroin seeking in both the food restricted and sated groups. In contrast, SCH 39166 (12.5 & 25.0 ng/side) in the NAc core selectively decreased the augmentation of heroin seeking in the food restricted group. These results suggest that cue-induced heroin seeking following withdrawal may be mediated by D1 receptor activation in the NAc shell, while the augmentation of heroin seeking induced by chronic food restriction may be specifically dependent on D1 receptor activation in the NAc core.

Disclosures: T.M. D'Cunha: None. **D. Rizzo:** None. **G. Mourra:** None. **M. Russo:** None. **F. Sedki:** None. **U. Shalev:** None.

Poster

781. Hedonia, Feeding, and Addictive Drugs

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Program#/Poster#: 781.08/J24

Topic: C.17. Drugs of Abuse and Addiction

Support: NIDA DA030425

NIMH MH091945

Title: Alternating access to a highly palatable diet and amphetamine sensitivity

Authors: *C. F. MOORE[1,2], V. SABINO[1], P. COTTONE[1];
[1]Lab. of Addictive Disorders, Departments of Pharmacol. and Psychiatry, [2]Grad. Program for Neurosci., Boston Univ., Boston, MA

Abstract: Eating disorders and certain forms of obesity are associated with mesolimbic dopaminergic reward dysfunction. Overeating of diets rich in sugar and fat alter dopamine neurotransmission in the nucleus accumbens, likely contributing to the persistence of excessive intake. Amphetamine-like drugs, which act in the mesolimbic pathway to enhance the release of dopamine, also confer long-lasting neuroadaptations. However, it is not yet known if a history of

disordered eating can alter sensitivity to these drugs. In this study, we investigated the effects of palatable food diet alternation on sensitivity to amphetamine challenges and amphetamine self-administration. Ad libitum diet alternation occurred for 5 weeks prior to any testing. One group was provided a chow diet 7 days a week, and a second group was provided chow 5 days a week followed by 2 days of access to a highly palatable, chocolate flavored, high-sucrose diet. While continuing diet alternation, we measured locomotor activity following an amphetamine challenge to test sensitivity during the 2 days of access to the palatable diet as well as when animals were withdrawn from palatable food. Following this within-subject amphetamine administration schedule, animals were allowed to self-administer amphetamine in water in the home cage. Rats withdrawn from intermittent access to palatable food exhibited pronounced hypophagia of the otherwise acceptable standard diet and overeating of palatable food upon renewed access. Further analysis is being conducted to understand how a history of overconsumption of palatable food might sensitize the mesolimbic pathway to the stimulatory effects of amphetamine-like drugs, and whether this may be augmented during periods of palatable food withdrawal.

Disclosures: C.F. Moore: None. **V. Sabino:** None. **P. Cottone:** None.

Poster

781. Hedonia, Feeding, and Addictive Drugs

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 781.09/J25

Topic: C.17. Drugs of Abuse and Addiction

Support: University of Wisconsin – Eau Claire Faculty/Student Research Collaboration

Title: Discriminative stimulus effects of naltrexone in rats with limited access to sucrose, saccharin, or water

Authors: J. L. HERRMANN[1], J. M. WARNER[1], C. C. THAI[1], *E. M. DE ROACH[1], K. A. TWAROSKI[1], A. J. STAUB[1], A. C. VIRNIG[1], A. S. LEVINE[2], D. C. JEWETT[1];
[1]Univ. of Wisconsin - Eau Claire, Eau Claire, WI; [2]Univ. of Minnesota, Minneapolis, MN

Abstract: In most operant discrimination paradigms, large doses of naltrexone (NTX) are typically required to establish NTX as a discriminative stimulus in opioid-naïve subjects. Chronic, but limited access to sucrose increases endorphin function in rats. We attempted to establish NTX as a discriminative stimulus in rats given limited access to sucrose, saccharin, or water. Rats were trained to lever press and were given access to sucrose (25% or 32%), saccharin (0.1%) or water for 12 hours a day for two weeks. Rats were then given daily injections of either

saline or NTX (3.2 mg/kg, 15 min PT) 1 hour after access to the solution. After the training session subjects were returned to their home cage for the remainder of the 12 hour-access period. Water was available for all subjects for the other 12 hours. In rats with 12 hours access to sucrose, NTX was reliability discriminated from saline in a mean of 72 sessions (Md = 63, range 27-135 sessions). No significant differences in acquisition of the NTX-saline discrimination or initial NTX dose-effect functions were noted between sucrose concentrations. NTX failed to serve as a discriminative stimulus in rats given access to saccharin or water solutions. These results provide further support for the notion that chronic sucrose consumption increases endogenous endorphin function.

Disclosures: **J.L. Herrmann:** None. **J.M. Warner:** None. **C.C. Thai:** None. **E.M. De Roach:** None. **K.A. Twaroski:** None. **A.J. Staub:** None. **A.C. Virnig:** None. **A.S. Levine:** None. **D.C. Jewett:** None.

Poster

781. Hedonia, Feeding, and Addictive Drugs

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Topic: C.17. Drugs of Abuse and Addiction

Support: IBRO-InEurope Short Stay Grants Program to MVMDB

Italian Ministry of University and Research under grants FIRB-RBFR12DELS to CC and to CDA

Title: Influence of the ovarian cycle and estradiol in frustration stress-induced binge-like palatable food consumption in female rats with a history of food restriction

Authors: *M. V. MICIONI DI BONAVENTURA[1], T. A. LUTZ[2], A. ROMANO[3], C. D'ADDARIO[4], L. ASARIAN[2], C. CIFANI[1];
[1]Univ. of Camerino, Sch. of Pharmacy, Pharmacol. Unit, Camerino, Italy; [2]Inst. of Vet. Physiol. and Ctr. for Integrated Human Physiol., Univ. of Zurich, Zurich, Switzerland; [3]Dept. of Physiol. and Pharmacol., Sapienza Univ. of Rome, Rome, Italy; [4]Fac. of Biosci. and Technol. for Food, Agr. and Envrn., Univ. of Teramo, Teramo, Italy

Abstract: Eating disorders show marked gender differences [1] and several epidemiologic studies suggest that binge eating episodes are more common in females than in males [2]. To further investigate the mechanisms underlying this sex difference, we used an animal model first

described by Cifani et al. [3], in which binge eating is evoked in female rats by food restriction followed by frustration stress (15 min exposure to the sight of the palatable food). We aimed to determine whether binge eating behavior varies across the estrus cycle and is influenced by estradiol in ovariectomized (OVX) rats. Finally, using immunocytochemistry, we quantified the activation of extracellular signal regulated kinase (ERK) signaling pathway in OVX rats treated with estradiol or oil vehicle, in basolateral (BLA) and the central (CeA) nuclei of the amygdala, paraventricular nucleus of hypothalamus (PVN) and arcuate nucleus (ARC). Restricted and stressed non-estrus rats showed binge eating behavior in comparison to the control not restricted and not stressed rats. This response was not present in restricted and stressed rats in estrus, and in OVX rats treated with estradiol. This lack of binge eating behavior was accompanied by a significant decrease in ERK phosphorylation in ARC, PVN and in the CeA, but not in BLA, in comparison to non-estrous rats and to not restricted and not stressed animals. Our behavioral findings show that binge eating does not occur during the estrous phase. Because this was recapitulated in OVX rats treated with estradiol, we propose that the inhibitory effect of estradiol on eating is partly responsible for the lack of bingeing. These findings are consistent with reports in women with bulimia nervosa [4], in whom the binge frequency decreased during the follicular phase, a time of the menstrual cycle when eating is also lowest. These results extend our previous findings and increase the validity of our model, such that it can be used in translational studies of the mechanism of binge eating behavior. References: [1] Klump et al. 2008 Psych Med 38:1749-57 [2] Cifani et al. 2009 Psychopharmology 204:113-125 [3] Hudson et al. 2007 Biol Psychiatry 61:348-358 [4] Edler et al. 2007 Psych Med 37:131-141

Disclosures: **M.V. Micioni Di Bonaventura:** None. **T.A. Lutz:** None. **A. Romano:** None. **C. D'Addario:** None. **L. Asarian:** None. **C. Cifani:** None.

Poster

781. Hedonia, Feeding, and Addictive Drugs

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 781.11/J27

Topic: C.17. Drugs of Abuse and Addiction

Support: PRVOUK 34

IGA NT 13687-3

260168/SVV/2015

Title: Changes of leptin and insulin plasma levels during different phases of morphine dependence in rats

Authors: T. HAVLICKOVA, P. JERABEK, P. POTMESIL, *M. SUSTKOVA;
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Abstract: Aims: An increasing number of studies over the past few years have explored relationship between appetite regulating hormones (including leptin and insulin), eating disorders and drug addiction with the hope of finding new therapeutic approach to addiction. So far, in the opioid addiction these relationships have been rarely investigated. The aim of our study was to monitor changes in plasma levels of leptin and insulin in various stages of morphine dependence in the rat model. Establishing of suspected correlations would suggest the participation of these hormones in the mechanisms of morphine addiction and thus support the idea of the possible use of these mechanisms in the development of new drugs for the treatment of opioid dependence. Methods: Blood samples were collected from the tail vein repeatedly five times: within the opioid group (11 rat males) (i) baseline sample, (ii) on the last day of repeated morphine (MO) administration before the last dose injection (MO was applied once daily in increasing doses 10, 20, 20, 40, 40 mg / kg s.c.), (iii) the third day of the spontaneous abstinence (during the somatic withdrawal symptoms), (iv) on the 10^{th}-12^{th} day of abstinence before the challenge MO (10 mg/kg) dose and (v) 1 hour after this challenge dose. Within the control group (6 rats) saline was applied repeatedly and MO challenge/acute dose (10 mg/kg) was administered on the last experimental day. Leptin and insulin were subsequently determined in the plasma using multi-ELISA. Results: In comparison with the control group and its own baseline values within the opioid group the levels of insulin and leptin were significantly decreased during the repeated MO administration and also during the MO withdrawal symptoms. These low plasma levels returned to the basal values during the long-term abstinence in case of leptin and insulin levels even significantly exceeded the baseline concentrations. Challenge MO dose during abstinence (as well as acute MO dose in the control group) induced a decrease of both peptides plasma levels. Conclusion: In both anorexigenic hormones plasma levels were found similar significant changes in the MO-dependence rat model, which indicate participation of both peptides in opioid dependence mechanisms. Thus further investigation into the role of leptin and insulin systems in opioid dependence is warranted.

Disclosures: **T. Havlickova:** None. **P. Jerabek:** None. **P. Potmesil:** None. **M. Sustkova:** None.

Poster

781. Hedonia, Feeding, and Addictive Drugs

Location: Hall A

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Program#/Poster#: 781.12/J28

Topic: F.02. Animal Cognition and Behavior

Support: NIH Director's New Innovator Award DP2DK105570-01

Pew Scholars Program

Klarman Family Foundation

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Davis Foundation Postdoctoral Fellowship

Title: Food-cue responses in amygdalo-cortical axons are modulated by hunger state

Authors: *C. R. BURGESS[1,2], R. N. RAMESH[1,2], K. M. LEVANDOWSKI[1], X. WANG[1], M. MINNIG[1], M. L. ANDERMANN[1,2];
[1]Endocrinol., Beth Israel Deaconess Med. Ctr., Boston, MA; [2]Harvard Univ., Boston, MA

Abstract: Hunger can selectively enhance attention to food-associated cues. In modern society, where food cues are ubiquitous, this can lead to increased food intake and adverse health effects. Human neuroimaging studies demonstrate hunger-specific modulation of neural activity in temporal cortex when viewing pictures of food cues, however, the neural mechanisms that underlie this bias to motivationally relevant stimuli are unclear. We used rabies tracing techniques to demonstrate strong reciprocal excitatory connections between temporal cortex and the lateral nucleus of the amygdala. Using two-photon microscopy, we imaged calcium activity in amygdala projections to temporal cortex in head-fixed mice performing a Go-NoGo task. We imaged the same amygdala axons across days to investigate how changes in hunger state would affect amygdala feedback to cortex. Amygdala responses to visual stimuli showed selectivity for salient visual cues and were modulated by hunger state. Specifically, we saw reduced activity in response to food cues when mice were sated. We propose that the lateral and basolateral amygdala, through reciprocal connections with temporal cortex, may bias attention to motivationally relevant environmental stimuli based on internal state.

Disclosures: C.R. Burgess: None. **R.N. Ramesh:** None. **K.M. Levandowski:** None. **X. Wang:** None. **M. Minnig:** None. **M.L. Andermann:** None.

Poster

781. Hedonia, Feeding, and Addictive Drugs

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 781.13/J29

Topic: C.17. Drugs of Abuse and Addiction

Support: Italian Ministry of University and Research under grants FIRB-RBFR12DELS to CC and to CDA

Title: Epigenetic regulation of adenosine A2A and dopamine D2 receptor gene transcription on compulsive food consumption

Authors: *C. CIFANI[1], M. V. MICIONI DI BONAVENTURA[1], M. PUCCI[2], M. GIUSEPPONI[1], C. LAMBERTUCCI[3], A. ROMANO[4], R. VOLPINI[3], M. MACCARRONE[5], C. D'ADDARIO[2];
[1]Univ. of Camerino, Sch. of Pharm., Camerino, Italy; [2]Fac. of Biosci. and Technol. for Food Agr. and Envrn., Univ. of Teramo, Teramo, Italy; [3]Sch. of Pharmacy, Medicinal Chem. Unit, Univ. of Camerino, Camerino, Italy; [4]Dept. of Physiol. and Pharmacol., Sapienza Univ. of Rome, Rome, Italy; [5]Univ. of Rome, Campus Bio-Medico, Rome, Italy

Abstract: Satisfactory treatments for eating disorders, such as binge eating disorder and bulimia nervosa, are not available at present. Using a well-characterized animal model of binge eating, we investigated the epigenetic regulation of the adenosine A2A receptor (A2AAR) and dopamine D2 receptor (D2R) gene. The animal model included four groups (rats fed normally, and then stressed or not, rats exposed to cycles of restriction/refeeding, and then stressed or not). Gene expression analysis carried out on the amygdala complex of restricted and stressed rats revealed a significant increase of A2AAR and D2R mRNA when compared to non-stressed and non-restricted rats. Administration of the A2AAR agonist (VT 7) induced in restricted and stressed rats a significant increase of A2AAR and D2R mRNA levels when compared to vehicle group, whereas a significant decrease in rats pre-treated with the A2AAR antagonist (ANR 94) was observed. Pyrosequencing analysis revealed a significant reduction of the % of DNA methylation at A2AAR promoter region in restricted and stressed rats compared to the non-stressed and non-restricted animals. We did not find any difference in D2R DNA methylation among different groups. Significant changes in the DNA methylation status of A2AAR promoter were found in restricted and stressed rats after administration of VT 7 or ANR 94. We observed a decrease of DNA methylation in VT 7 treated rats and a hypermethylation in ANR 94 rats with respect to the vehicle group. The increase in A2AAR mRNA observed in restricted and stressed rats could be due to a compensatory mechanism to counteract the effect of binge eating, suggesting that the A2AAR activation, inducing receptor gene up-regulation, could be relevant to reduce food consumption. We here demonstrated for the first time the epigenetic regulation of A2AAR in an animal model of binge eating.

Disclosures: **C. Cifani:** None. **M.V. Micioni Di Bonaventura:** None. **M. Pucci:** None. **M. Giusepponi:** None. **C. Lambertucci:** None. **A. Romano:** None. **R. Volpini:** None. **M. Maccarrone:** None. **C. D'Addario:** None.

Poster

781. Hedonia, Feeding, and Addictive Drugs

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Topic: C.17. Drugs of Abuse and Addiction

Support: CONACYT. Project 168236.

Title: Metabotropic glutamate receptors 2,3 modulate addiction to fat food intake in mice

Authors: ***A. CAMACHO**, L. MONTALVO, C. VEGA HERRERA;
Univ. Autónoma De Nuevo León, Nuevo León, Mexico

Abstract: Introduction: Obesity is a health problem worldwide. It has been proposed that obesity development results of addictive consumption of energy-dense palatable foods. Drug addiction establishment requires changes in synaptic plasticity in the reward system involving the expression of 2.3 metabotropic glutamate receptors (mGlur 2,3), N-methyl-D-aspartate receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor and dopamine D2 receptors. We determine whether modulation of mGlur 2,3 prevents fat food addiction. Material and Methods: We used conditioned place preference (CPP) test to determine fat food addiction. mGluR2,3 and dopamine D2 receptors was determine by western blot in the nucleus accumbens (Nac). To determine if the role of mGlur2,3 on preference for fat food consumption in mice we intraperitoneally administered mGlur2,3 agonist LY379268. We evaluated the effect of LY379268 on behavior and fat food addiction using CPP test. Results: Mice showed that fat food exposure results in positive CPP score during the test. The preference for fatty food intake correlates with decrease in rGlum2,3 protein levels in the Nac of addicted mice. Addicted mice showed no change in body weight, plasma or blood glucose, insulin and leptin, relative to control mice. Of importance, the administration of the mGlur2,3 agonist LY379268 seems to modulate preference for fatty food intake compared to vehicle administration. Conclusions: Our data suggest that the function of mGlur2,3 is relevant and potentially adaptable to prevent addiction to appetizing food.

Disclosures: **A. Camacho:** None. **L. Montalvo:** None. **C. Vega Herrera:** None.

Poster

781. Hedonia, Feeding, and Addictive Drugs

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Topic: C.17. Drugs of Abuse and Addiction

Support: DA030425

MH091945

MH093650

Title: Binge-like eating as an addiction-like disorder: novel findings from an operant model in rats

Authors: *C. HICKS, C. VELÁZQUEZ-SÁNCHEZ, J. W. SANTOS, K. L. SMITH, A. FERRAGUD, V. SABINO, P. COTTONE;
Pharmacol. and Exptl. Therapeut., Boston Univ. Sch. of Med., Boston, MA

Abstract: Binge eating disorder is characterized by excessive consumption of highly palatable food within short periods of time accompanied by loss of control over eating. Extensive evidence provides support for the consideration of binge eating disorder as an addiction-like disorder. In this study, we wanted to determine whether rats undergoing an operant binge-like eating procedure could develop maladaptive forms of conditioned feeding behaviors. We also wanted to determine whether the binge eating procedure could alter dopamine D2 receptor (D2R) levels in key brain regions implicated in drug and natural reward processing. For this purpose, we trained male rats to self-administer either a sugary, highly palatable diet ("Palatable" rats) or a chow diet ("Chow" rats) for 1 hour a day. After escalation and stabilization of palatable food intake, we tested Chow and Palatable rats in (a) a conditioned place preference test, (b) a second-order schedule of reinforcement and (c) a cue-induced suppression of feeding test. In the conditioned place preference task, Palatable rats spent significantly more time in the compartment that was previously paired with the palatable food, compared to Chow controls. Furthermore, in the second-order schedule of reinforcement task, Palatable rats exhibited active lever responding 4- to 6-fold higher than Chow control rats. In addition, in the cue-induced suppression of feeding test, although Chow control subjects reduced responding by 32% in the presence of the conditioned punishment, Palatable rats persevered in responding despite the aversive cue. Finally, following exposure to the palatable diet, binge-eating rats showed reduced D2R levels in prefronto-cortical regions of the brain. These results further characterize this animal model of

binge-like eating and provide additional evidence for the addictive properties of highly palatable food.

Disclosures: **C. Hicks:** None. **C. Velázquez-Sánchez:** None. **J.W. Santos:** None. **K.L. Smith:** None. **A. Ferragud:** None. **V. Sabino:** None. **P. Cottone:** None.

Poster

782. Monoaminergic Plasticity in Addiction

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 782.01/J32

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: DePauw University

Title: Nicotine-induced locomotor behavior in zebrafish larvae: function of 5-HT2A and 5-HT2C receptors

Authors: *H. SCHNEIDER[1], E. M. BUENING[2], Y. LIU[2], E. E. CLOR[2], K. Y. CHEN[2], B. F. KOPECKY[2], N. J. SNYDER[2], S. OWIREDU[2], S. INDIA-ALDANA[2], R. A. MILLER[2], S. RAMAYADAN[2], C. O. HASKEN[2], P. SURESH[2], D. HUYNH[2];
[1]Dept. of Biol., Depauw Univ., Greencastle, IN; [2]DePauw Univ., Greencastle, IN

Abstract: The ultimate goal of our studies is to find chemicals that help people quit smoking. Zebrafish larvae allow the screening of large number of chemical compounds in simple neurobehavioral assays and could represent a potential model for the initial identification of pharmacotherapeutics for smoking cessation treatment. In mammals, serotonin receptors of type 2a (htr2a) and 2c (htr2c) have been implicated in regulating different states of tobacco dependence, thus representing potential targets for treating tobacco dependence. Unclear is how nicotine functions in larval zebrafish compared to rodents and if serotonin receptors are involved in nicotine-induced behavior in zebrafish larvae in a similar way as in rodents. To develop a model of nicotine function and htr function in nicotine-induced behavior in zebrafish larvae a locomotion-based assay for has been used. Expression of htrs was detected using *in situ* hybridization, immunocytochemistry, or RT-PCR. Chemicals such as varenicline, the active chemical used for treating smoking cessation, reduces the acute nicotine-induced locomotor response without detrimental effects in larval zebrafish. A potential role of htrs in regulating nicotine-induced locomotor behavior was measured by pretreating larval zebrafish with selected htr2a and htr2c agonists and antagonists. The htr2c agonist lorcaserin showed the most effective reduction of nicotine-induced locomotor behavior with the least detrimental effects of all tested

agonists and antagonists. In contrast, tested htr2a agonists did not seem to change the acute nicotine response significantly. Exposure to nicotine before pretreatment with htr agonists and antagonists, changes the outcome of neurobehavioral experiments. To rule out detrimental effects of tested chemicals, acute mustard oil-induced locomotor responses were measured. Pharmacological characterization of zebrafish serotonin receptors will indicate functional similarities with mice serotonin receptors. In summary, the project further supports a role of serotonin receptors in nicotine-induced behavior in larval zebrafish and shows that the activation of htr2c receptors in zebrafish reduces the nicotine-induced motor behavior.

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Poster

782. Monoaminergic Plasticity in Addiction

Location: Hall A

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Topic: C.17. Drugs of Abuse and Addiction

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Institute for Translation Sciences at UTMB

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Center for Addiction Research at UTMB

Title: Exploring a putative protein:protein interaction between the serotonin (5-HT) 5-HT2A receptor (5-HT2AR) and 5-HT2CR

Authors: ***C. E. MCALLISTER**[1], N. C. ANASTASIO[2,1], S. J. STUTZ[1], R. M. HARTLEY[1], L. H. FINK[1], B. FONGANG[3], A. KUDLICKI[3], S. R. GILBERTSON[4,1], Y.-C. CHEN[4], H. NEELANKANTAN[1], C. S. WATSON[3,1], F. G. MOELLER[5], K. A. CUNNINGHAM[2,1];

[1]Ctr. for Addiction Res., [2]Dept. of Pharmacol. and Toxicology, [3]Dept. of Biochem. and Mol. Biol., Univ. of Texas Med. Br., Galveston, TX; [4]Dept. of Chem., Univ. of Houston, Houston, TX; [5]Dept. of Psychiatry, Virginia Commonwealth Univ. Sch. of Med., Richmond, VA

Abstract: The serotonin (5-HT) 5-HT2A receptor (5-HT2AR) and 5-HT2CR play important roles in behavior and physiology. We have recently demonstrated that knockdown of 5-HT2CR following microinjection of 5-HT2CR shRNA into the rat medial prefrontal cortex (mPFC) evokes a behavioral phenotype characterized by increased motor impulsivity and elevated reactivity to cues associated with cocaine self-administration. The 5-HT2CR knockdown in mPFC also resulted in upregulation of 5-HT2AR protein in the mPFC and a leftward shift in potency of systemic M100907 to suppress motor impulsivity, suggesting a functional disruption of local 5-HT2AR:5-HT2CR balance. Furthermore, co-immunoprecipitation studies suggested that a protein:protein interaction exists between 5-HT2AR and 5-HT2CR in mPFC. In the present study, we employed immunohistochemistry, proximity ligation assay (PLA), and luciferase complementation assay (LCA) technologies in either live cells and/or rat brain, as well as the in silico direct coupling analysis (DCA), to test the hypothesis that a protein:protein interaction occurs between the 5-HT2AR and 5-HT2CR. In immunohistochemical analyses, we found that 5-HT2AR and 5-HT2CR protein co-localized within the same cells in rat mPFC. In the PLA (Duolink), we found that native, unmodified proteins are in close proximity (<45 nm) in mPFC. In the DCA (which examines the co-evolution of residues in over 100 species), we identified candidate pairs of amino acid residues that are predicted to be in direct functional contact, most notably between the extracellular N-terminus domains of the two proteins. The LCA is being employed to test the hypothesis that the N-terminal domains are the primary points of interaction between the two receptors. In the LCA, two complementary luciferase N- (NLuc) and C-terminus (CLuc) fragments, which have no activity on their own, are fused to the two receptor proteins of interest, respectively. In the presence of the substrate D-luciferin, association of the two proteins brings the inactive fragments into close proximity to reconstitute the enzyme activity. We are co-expressing 5-HT2AR-NLuc (or CLuc) and 5-HT2CR-CLuc (or NLuc), expressed on the N-or C-terminus in mammalian cells to demonstrate the formation of a protein:protein interaction between the 5-HT2AR and 5-HT2CR in live cells. We will treat the cells with a peptide which is predicted by the DCA to disrupt the interaction and impact cellular signaling. To date, our findings suggest that 5-HT2AR:5-HT2CR protein interaction may provide a new neurobiological mechanism underlying behavior and a possible target for novel pharmacotherapuetics, such as heterobivalent ligands.

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Poster

782. Monoaminergic Plasticity in Addiction

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Support: P50DA033935

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K99DA033374

Title: Serotonin (5-HT) 5-HT_{2A} receptors in the medial prefrontal cortex regulate cue reactivity following prolonged forced abstinence from cocaine self-administration

Authors: *H. NEELAKANTAN[1], N. C. ANASTASIO[1,2], R. G. FOX[1], S. J. STUTZ[1], K. A. CUNNINGHAM[1,2];
[1]Ctr. for Addiction Res., [2]Pharmacol. and Toxicology, Univ. of Texas Med. Br. Galveston, Galveston, TX

Abstract: An intensification of craving in humans and reactivity to drug-associated cues in rodents occurs during abstinence while elevation of cue reactivity ("incubation") is observed in rats exposed to prolonged periods of forced abstinence from cocaine self-administration. Incubation in rodents has been linked to time-dependent neuronal plasticity in the medial prefrontal cortex (mPFC). The mPFC expresses the serotonin (5-HT) 5-HT_{2A} receptor (5-HT_{2A}R) and blockade of the mPFC 5-HT_{2A}R suppresses cue reactivity. We have demonstrated that membrane expression of the 5-HT_{2A}R protein in the mPFC predicts levels of cue reactivity [lever presses reinforced by the discrete cue complex (e.g., stimulus light, pump tone)] following cocaine self-administration in rats. With regard to incubation, we found that expression of the 5-HT_{2A}R is elevated in membrane extracts of the mPFC on Day 30 *vs.* Day 1 of forced abstinence from cocaine self-administration. This observation prompted us to test the hypothesis that rats will be more sensitive to the effects of a selective 5-HT_{2A}R antagonist (M100907) to suppress cue reactivity on Day 30 *vs.* Day 1 of forced abstinence. Rats were trained to self-administer cocaine for 14 days (0.75 mg/kg/inf, FR5) and the effects of M100907 (0.03-0.3 mg/kg, i.p.) on cue reactivity were measured on Day 1 and Day 30 of forced abstinence. Cue reactivity was significantly elevated on Day 30 *vs.* Day 1 of forced abstinence. Pharmacological analysis revealed that all doses of M100907 (0.03-0.3 mg/kg) significantly ($p<0.05$) suppressed cue reactivity during prolonged (Day 30), but not early abstinence (Day 1). These data suggest that the elevated expression of membrane 5-HT_{2A}R protein in the mPFC on Day 30 may contribute mechanistically to the time-dependent incubation of cue reactivity following forced abstinence.

Mechanistically linking 5-HT_{2A}R regulatory mechanisms to time-dependent incubation phenomena will have direct clinical implications in developing 5-HT_{2A}R-targeted therapeutics to minimize vulnerability to relapse in cocaine use disorder.

Disclosures: H. Neelakantan: None. **N.C. Anastasio:** None. **R.G. Fox:** None. **S.J. Stutz:** None. **K.A. Cunningham:** None.

Poster

782. Monoaminergic Plasticity in Addiction

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Topic: C.17. Drugs of Abuse and Addiction

Support: DA033935

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John Sealy Memorial Endowment Fund

Center for Addiction Research

Title: Serotonin (5-HT) 5-HT_{2A} receptor (5-HT_{2A}R):5-HT_{2C}R protein interaction as a therapeutic target: Novel 5-HT_{2A}R antagonist/5-HT_{2C}R agonist heterobivalent ligands as neuroprobes

Authors: *R. M. HARTLEY[1], N. C. ANASTASIO[1,2], S. R. GILBERTSON[1,4], Y.-C. CHEN[4], R. G. FOX[1], S. J. STUTZ[1], L. H. FINK[1], S. E. SWINFORD-JACKSON[1], C. S. WATSON[1,3], F. G. MOELLER[5], K. A. CUNNINGHAM[1,2];
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Abstract: A feature of multiple neuropsychiatric disorders is motor impulsivity. Recent studies have implicated 5-HT system in medial prefrontal cortex (mPFC) in mediating individual differences in motor impulsivity, notably the 5-HT_{2A}R and 5-HT_{2C}R. We investigated the

hypothesis that differences in the ratio of 5-HT_{2A}R:5-HT_{2C}R in mPFC would predict the individual level of motor impulsivity. Native protein levels of the 5-HT_{2A}R and the 5-HT_{2C}R predicted the intensity of motor impulsivity and the 5-HT_{2A}R:5-HT_{2C}R ratio in mPFC tracked with levels of premature responses in individual outbred rats. The possibility that the 5-HT_{2A}R and 5-HT_{2C}R act in concert to control motor impulsivity is supported by the observation that high motor impulsivity associated with a diminished mPFC synaptosomal 5-HT_{2A}R:5-HT_{2C}R protein interaction. We infer that there is an interactive relationship between the mPFC 5-HT_{2A}R and 5-HT_{2C}R, and that a 5-HT_{2A}R:5-HT_{2C}R imbalance may be a functionally-relevant mechanism underlying motor impulsivity. Based on these findings, we propose that correcting this imbalance and stabilizing the 5-HT_{2A}R:5-HT_{2C}R protein interaction utilizing a ligand with dual action as a selective 5-HT_{2A}R antagonist (e.g., M100907)/5-HT_{2C}R agonist (e.g., WAY163909) presents a promising and novel pharmacotherapeutic strategy for treatment of brain disorders in which motor impulsivity is implicated. We identified benign tether locations on M100907 and WAY163909 and used click chemistry to synthesize a series of M100907:WAY163909 heterobivalent ligands. We employed quantitative live cell assays to measure two types of signaling evoked by ligand activation, Ca_i^{++} release and phosphorylation of $ERK_{1/2}$. In the 5-HT_{2A}R-CHO-K1 cell line, the heterobivalent ligand inhibited 5-HT-induced Ca_i^{++} release with IC_{50}s ranging from 125-210 nM. In the 5-HT_{2C}R-CHO-K1 cell line, the heterobivalent ligands demonstrated no intrinsic activity, however, in the dual expressing 5-HT_{2A+2C}R-CHO-K1 cell line, the heterobivalent ligands inhibited 5-HT-induced Ca_i^{++} release with IC_{50}s between 438-725 nM. Interestingly, the heterobivalent ligands appear to act as partial agonists given their ability to phosphorylate $ERK_{1/2}$ in the 5-HT_{2A+2C}R-CHO-K1 cell line, demonstrating a novel pharmacological profile *in vitro*. Extensive behavioral analyses are currently underway to evaluate our novel heterobivalent molecules *in vivo*. These data provide the first profile of heterobivalent 5-HT_{2A}R antagonist/5-HT_{2C}R agonist ligands which will be useful as neuroprobes and potentially useful to develop treatment strategies for brain disorders in which impulsivity is a factor.

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Poster

782. Monoaminergic Plasticity in Addiction

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Topic: C.17. Drugs of Abuse and Addiction

Support: DA035620

DA024157

DA033935

DA033374

DA022506

DA006511

DA020087

Title: Dynamic regulation of synaptosomal serotonin (5-HT) 5-HT_{2C} receptor (5-HT_{2C}R) expression following acute cocaine administration

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Abstract: Activation of the 5-HT_{2C}R in the medial prefrontal cortex (mPFC) regulates cocaine-seeking assessed in the cocaine self-administration/forced abstinence assay in rats. The functional impact of 5-HT_{2C}R activation is mechanistically controlled by a complement of factors, including subcellular localization of the receptor. Previous studies indicate that the 5-HT_{2C}R is poised to influence the synaptosomal milieu in the mPFC and interfaces in a functionally-coordinated manner with synaptic proteins to promote or inhibit receptor readiness and subsequent signaling capacity. We previously demonstrated that synaptosomal 5-HT_{2C}R expression in the mPFC on Day 30 of forced abstinence is lower than on Day 1, suggesting that regulation of the 5-HT_{2C}R in mPFC may be a mediator of elevated cue-elicited cocaine-seeking in late abstinence from cocaine self-administration. Interestingly, the levels of 5-HT_{2C}R expression in the synaptosomal compartment of the mPFC of naïve rats mirrors those assessed at Day 30; levels observed at Day 1 are significantly elevated relative to naïves. These data suggest that 5-HT_{2C}R protein expression, and perhaps subcellular localization of the receptor, are responsive to the pharmacological environment consequent to recent self-administration of cocaine and/or acute withdrawal. In the present study, we tested the hypothesis that acute pretreatment with or withdrawal from non-contingent cocaine will increase synaptosomal 5-HT_{2C}R expression in a time-dependent manner. Male Sprague-Dawley rats were injected with saline (0.9%; i.p.) or cocaine (15 mg/kg; i.p.) 15 min or 24 hrs prior to sacrifice and mPFC harvest. Crude synaptosomal protein was extracted from the mPFC and 5-HT_{2C}R protein expression was measured using a novel medium-throughput 96-well plate immunoassay adapted

for use with brain tissue in our laboratory. The plate immunoassay is highly reliable, reproducible and amenable to assaying multiple conditions in the same experiment. We found that synaptosomal 5-HT_{2C}R expression in mPFC was elevated 15 min following cocaine vs. saline administration; analyses at 24 hrs of withdrawal are in progress. Ongoing experiments are exploring the association of the 5-HT_{2C}R with synaptic protein partners (e.g. G proteins vs. β-arrestins) which regulate its trafficking and function. Understanding the dynamic regulation of 5-HT_{2C}R expression following acute cocaine administration is a critical first step toward exploring the effects of chronic cocaine-taking and withdrawal on 5-HT_{2C}R expression, which will ultimately inform the development of effective pharmacotherapeutics to treat cocaine use disorder.

Disclosures: **S.E. Swinford-Jackson:** None. **N.C. Anastasio:** None. **C.A. Soto:** None. **R.M. Hartley:** None. **C.S. Watson:** None. **K.A. Cunningham:** Other; Dr. Cunningham is a consultant for Arena Pharmaceuticals..

Poster

782. Monoaminergic Plasticity in Addiction

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Topic: C.17. Drugs of Abuse and Addiction

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UTMB Center for Addiction Research

Title: Individual differences in impulsive action in rats are governed by cortical N-methyl-D-aspartate receptor (NMDAR) tone

Authors: *C. KREBS, N. ANASTASIO;
UTMB, Galveston, TX

Abstract: Impulsivity is a complex, multifaceted trait broadly defined as action without sufficient foresight; high inherent impulsivity may increase the likelihood that drug use escalates into dependence and relapse. Glutamate neurotransmission within the medial prefrontal cortex (mPFC) may critically regulate the cognitive and/or behavioral dimensions underlying impulsivity. The N-methyl-D-aspartate receptor (NMDAR) is a member of the ionotropic glutamate receptor family and is composed of multiple subunits including GluN1 and GluN2A-D. Noncompetitive antagonism of the NMDAR and selective antagonism of the GluN2B subunit

enhances impulsivity in animal models. Here, we tested the hypothesis that differences in NMDAR subunit composition and signaling deficits within the mPFC mediate high inherent impulsivity, and that pharmacological potentiation of NMDAR signaling attenuates high inherent impulsivity. Outbred male Sprague Dawley rats were identified as high (HI) or low (LI) impulsive using the one-choice serial reaction time (1-CSRT) task. In this task, nose-pokes after presentation of a visual stimulus resulted in food pellet delivery. Nose-pokes before presentation of the visual stimulus (i.e., premature responses) indexed impulsive action. A quartile split based on the number of premature responses was used to identify HI or LI rats. Following phenotypic identification, mPFC synaptosomal protein was extracted from a cohort of HI and LI rats to assess NMDAR composition via immunoblotting. A separate cohort of HI and LI rats were trained to criterion on the 1-CSRT task, and on test days, pretreated with vehicle (saline, 1 ml/kg; i.p.) or D-cycloserine (DCS; agonist at strychnine-insensitive glycine site of NMDAR; 1-50 mg/kg, i.p.). Performance on the 1-CSRT task was rapidly acquired and allowed stable identification of HI and LI rats; premature responses in HI rats remained significantly higher than LI rats across 70 training days ($p<0.001$). HI rats had lower mPFC GluN1 and GluN2A synaptosomal protein expression compared to LI rats ($p<0.05$). No difference in GluN2B levels was detected between HI and LI rats. Select doses of DCS decreased premature responses relative to saline administration in HI, but not LI, rats ($p<0.05$). Taken together, inherent impulsive action may be critically driven by dysregulation of mPFC GluN1/GluN2A signaling and selective potentiation of NMDAR function may rescue high inherent impulsive action. Increased understanding of the neurobiology underlying inherent differences in impulsivity may aid development of pharmacotherapies that target drug dependence, relapse, and other disorders characterized by impulsivity.

Disclosures: **C. Krebs:** None. **N. Anastasio:** None.

Poster

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K05 DA020087

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Klarman Family Foundation

Title: Activation of the corticoaccumbens circuit attenuates inherent impulsivity and binge intake of high fat food

Authors: *N. C. ANASTASIO[1,2], S. J. STUTZ[1], A. E. PRICE[1], S. M. FERGUSON[3], J. F. NEUMAIER[4], K. A. CUNNINGHAM[1,2];
[1]Ctr. for Addiction Res., [2]Pharmacol. and Toxicology, Univ. Texas Med. Br., Galveston, TX; [3]Psychiatry, Seattle Children's Res. Inst., Seattle, WA; [4]Psychiatry and Behavioral Sci., Univ. of Washington Sch. of Med., Seattle, WA

Abstract: Eating is essential for life, but repeated consumption of large amounts of food in a brief period (i.e., bingeing) can alter the reward value of food and food-related cues and fuel binge-eating cycles. Impulsivity, a predisposition toward rapid unplanned reactions to stimuli, is one of the multifaceted determinants underlying the etiology of dysregulated eating, its pathogenesis, and treatment outcomes. The medial prefrontal cortex (mPFC) is a major neural director of reward-driven behavior, impulse control and integration of internal states with environmental cues. Compromised signaling between the mPFC and nucleus accumbens (NAc) are thought to underlie the cognitive inability to withhold prepotent responses (impulsive action) and binge intake of high fat food. We propose that strategies to directly activate this circuit would indicate that the ventral infralimbic (IL)-nucleus accumbens shell (NAcSh) pathway plays a putative suppressive role ("Stop") in impulsive action and binge eating. We employed a dual viral vector technology that allows for the targeted and isolated modulation of IL mPFC neurons that project to the NAcSh via a Cre-loxP system. A Cre-dependent viral vector based "double-floxed" inverted open reading frame (DIO) switch system expresses an engineered Gq-DREADD which only binds clozapine-N-oxide (CNO). In the presence of Cre, the loxP sites are excised and the transgene is inverted into the sense direction and expressed from the hSyn promoter. An AAV DIO construct that contains an inverted version of Gq DREADD (hM3D)-mCherry or mCherry alone was infused into the IL mPFC. A canine adenovirus-2 (CAV)-Cre axonal retrograde viral vector was infused into the NAcSh of the same rat; stable transgene expression in IL mPFC occurred only at the site of DIO vector infusions thus restricting expression to cortical neurons that project to the NAcSh. Activation of the circuit with DIO-hM3D-mCherry AAV in the presence of CNO significantly suppressed impulsive action in the 1-choice serial reaction time task ($p<0.05$); no differences in task acquisition, accuracy, omissions or additional task parameters were observed. The DIO-hM3D-mCherry-AAV in the presence of CNO significantly decreased binge intake for high fat food ($p<0.05$). These data indicate that impulsive action and binge eating reciprocally interact at the level of an imbalance in homeostasis within the corticoaccumbens circuit. Through addressing a fundamental gap in our knowledge of how the neural aspects of impulsivity relate to binge eating, we hope to develop pharmacological strategies to minimize binge eating and enhance clinical practice for disorders of overeating.

Disclosures: **N.C. Anastasio:** None. **S.J. Stutz:** None. **A.E. Price:** None. **S.M. Ferguson:** None. **J.F. Neumaier:** None. **K.A. Cunningham:** None.

Poster

782. Monoaminergic Plasticity in Addiction

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Title: Programming of dopaminergic neurons by neonatal sex hormone exposure: Effects on dopamine content and tyrosine hydroxylase expression in adult male rats

Authors: P. ESPINOSA, R. A. SILVA, R. RIQUELME, L. F. GONZALEZ, N. K. SANGUINETTI, F. C. VENEGAS, G. CRUZ, G. M. RENARD, P. R. MOYA, *R. SOTOMAYOR-ZÁRATE;
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Abstract: We sought to determine the long-term changes produced by neonatal sex hormone administration on the functioning of midbrain dopaminergic neurons in adult male rats. Sprague-Dawley rats were injected subcutaneously at postnatal day 1 and were assigned to the following experimental groups: TP (testosterone propionate 1.0 mg/50μL); DHT (dihydrotestosterone 1.0mg/50μL); EV (estradiol valerate 0.1 mg/50μL) and control (sesame oil 50μL). At postnatal day 60, neurochemical studies were performed to determine dopamine content in substantia nigra-ventral tegmental area and dopamine release in nucleus accumbens. Behavioral (basal and amphetamine-induced locomotor activity) and molecular (mRNA expression of tyrosine hydroxylase) studies were also performed. We found increased dopamine content in substantia nigra-ventral tegmental area of TP and EV rats favoring dopamine release in nucleus accumbens. However, neonatal exposure to DHT, a non-aromatizable androgen, did not affect midbrain dopaminergic neurons. Correspondingly, the levels of tyrosine hydroxylase mRNA were significantly increased in TP and EV rats, but not in DHT and control rats. Our results suggest a mechanism involving increased tyrosine hydroxylase expression through aromatization of testosterone to estradiol in substantia nigra-ventral tegmental area.

Disclosures: **P. Espinosa:** None. **R.A. Silva:** None. **R. Riquelme:** None. **L.F. Gonzalez:** None. **N.K. Sanguinetti:** None. **F.C. Venegas:** None. **G. Cruz:** None. **G.M. Renard:** None. **P.R. Moya:** None. **R. Sotomayor-Zárate:** None.

Poster

782. Monoaminergic Plasticity in Addiction

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIH Grant DA035468

Title: Embryonic methamphetamine exposure inhibits methamphetamine cue conditioning and reduces dopamine tissue levels in adult wild-type *C. elegans*

Authors: S. N. KATNER[1], E. A. ENGLEMAN[1], *B. S. NEAL-BELIVEAU[2];
[1]Psychiatry, Indiana Univ. Sch. of Med., Indianapolis, IN; [2]Psychology, IUPUI, Indianapolis, IN

Abstract: Methamphetamine (MAP) addiction is a serious and costly disorder leading to thousands of deaths and costing billions of dollars annually. A disturbing outcome of MAP addiction is the uncontrolled embryonic exposure to this drug and the effects on brain development and behavioral consequences later in life. Although studies have begun to provide important information about some aspects of the neurobiology of MAP addiction, very little research has focused on these developmental issues and few good developmental models are available. *C. elegans* is an excellent model organism to study the neurobiological consequences of embryonic MAP exposure. It has a well studied and described neuroanatomical system, along with a short generation time for fast generation of data at a fraction of the cost of many other organisms. The objective of the current study was to determine the long-term behavioral and neurochemical effects of embryonic MAP exposure in *C. elegans*. Wild-type N2 worms were embryonically-exposed to 50 μM MAP or vehicle. Using classical conditioning, embryonically-exposed worms were conditioned to MAP (17 and 500 μM) as adults in the presence of either sodium (Na^+) or chloride (Cl^-) ions as conditioned stimuli (CS+/CS-). Following conditioning, a preference test was performed by placing worms in 6-well test plates spotted with the CS+ and CS- at opposite ends of each well. A food conditioning experiment was also performed to determine if embryonic MAP exposure affected food conditioning behavior. For the neurochemical experiments, adult worms that were embryonically-exposed to MAP were analyzed for dopamine (DA) content using high performance liquid chromatography. Pairing an ion with 17 and 500 μM MAP significantly increased the preference for that ion (CS+) by 181 ±

15 % and 176 ± 18 % of controls, respectively, in worms that were *not* pre-exposed to MAP. However, worms embryonically-exposed to MAP did not exhibit significant drug cue conditioning. The inability of MAP-exposed worms to condition to MAP was not associated with deficits in food conditioning, as MAP-exposed worms exhibited a significant cue preference associated with food. Furthermore, embryonic MAP exposure reduced DA levels by 28 to 37% of baseline levels in adult *C. elegans*, which could be a key mechanism contributing to the long-term effects of embryonic MAP exposure. Overall, these data suggest that embryonic MAP exposure selectively reduces the reinforcing properties of MAP in adult *C. elegans,* which may be driven in part by concomitant decreases in DA levels. *Supported by DA035468(EAE).*

Disclosures: **S.N. Katner:** None. **E.A. Engleman:** None. **B.S. Neal-Beliveau:** None.

Poster

782. Monoaminergic Plasticity in Addiction

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Conacyt scholarship 38580

Title: Role of serotonin and dopamine neurotransmission in psychosis-like behaviors induced by toluene

Authors: *M. T. RIVERA-GARCÍA, C. LÓPEZ-RUBALCAVA, S. L. CRUZ;
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Abstract: Toluene-based products are commonly misused by inhalation for recreational purposes. Toluene has hallucinogenic effects, exacerbates psychosis symptoms in patients, and induces psychosis-like behaviors in rats. Among several molecular targets, toluene acts as a non-competitive NMDA receptor antagonist and alters serotonin (5-HT) and dopamine (DA) levels, but there are few studies analyzing the relationship between neurochemical changes and toluene-induced psychotomimetic actions. The present study examines the involvement of D_2 and 5-$HT_{2A/2C}$ receptors in changes in brain 5-HT and DA levels and psychosis-like behaviors produced by toluene. Male Wistar rats were exposed to toluene (4000 and 8000 ppm) for 30 min in a static exposure chamber. The $5HT_{2A/2C}$ mediated head-twitch response (Htr) was analyzed during toluene exposure. Immediately after, the striatum and prefrontal cortex were dissected and

analyzed by HPLC for DA and 5-HT contents. Independent groups of animals were evaluated in prepulse inhibition (PPI) or social interaction tests after toluene inhalation. In order to study the role of D_2 and 5-$HT_{2A/2C}$ receptors in toluene's effects, other groups of animals were pretreated (-20 min) with ketanserine (2 mg/kg) or haloperidol (1 mg/kg), exposed to toluene and tested in different trials. Toluene concentration-dependently increased DA and 5-HT contents in both brain areas. Haloperidol (1 mg/kg) and ketanserine (2 mg/kg) significantly reduced these effects. Toluene also induced a deficit in PPI, which was completely prevented by haloperidol and significantly blocked by ketanserine. Toluene-treated animals reduced contact behaviors with partners in social interaction test, and this effect was partially blocked by ketanserine, but not by haloperidol. Finally, toluene increased Htr in a concentration-dependent manner, this behavior was blocked equally by $5HT_{2A/2C}$ and D_2 receptor antagonism. Our results show that antipsychotic drugs can prevent some neurochemical and behavioral effects produced by toluene.

Disclosures: M.T. Rivera-García: None. **C. López-Rubalcava:** None. **S.L. Cruz:** None.

Poster

782. Monoaminergic Plasticity in Addiction

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Topic: B.01. Neurotransmitters and Signaling Molecules

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NIDA IRP

Title: Differential effects of translin deletion on behavioral and biochemical responses to cocaine and amphetamine

Authors: X. FU[1], M. NIWA[1], D. FUKUDOME[1], Y. CHERN[2], J. CADET[3], A. SAWA[1], *J. M. BARABAN[1];
[1]Johns Hopkins Univ. Sch. Med., Baltimore, MD; [2]Inst. of Biomed. Sci., Academica Sinica, Taipei, Taiwan; [3]NIDA IRP, Baltimore, MD

Abstract: To help define the role of the microRNA system in regulating neuronal signaling, we have studied the impact of translin deletion on the dopamine system. Translin and its partner protein, trax, form an RNAse complex that mediates degradation of microRNAs (Asada et al., Cell Reports, 2014). Accordingly, we have used translin KO mice to assess the role of the microRNA system in dopamine signaling. We have found that the classic ability of cocaine to

increase open field exploration is markedly inhibited in these mice. Furthermore, the ability of cocaine to increase nucleus accumbens dopamine levels as monitored by microdialysis is severely compromised. Accordingly, these findings suggest that elevated microRNA levels caused by translin deletion impair dopamine release from mesolimbic dopamine neurons. In contrast, the locomotor response to amphetamine is increased in these mice, while the ability of amphetamine to elevate dopamine levels in the nucleus accumbens is normal. These findings indicate that the enhanced locomotor response to amphetamine is due to post-synaptic supersensitivity to dopamine, which may be secondary to reduced dopamine tone. Current studies are aimed at assessing whether reinstatement of translin expression in VTA dopamine neurons is sufficient to rescue these phenotypes. In summary, these findings suggest that inhibition of the translin/trax complex provides a novel means of decreasing dopamine tone and may have therapeutic potential by promoting resilience in the face of chronic stress.

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Poster

782. Monoaminergic Plasticity in Addiction

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Topic: C.17. Drugs of Abuse and Addiction

Title: Involvement of orexin-2 receptors within the ventral tegmental area in development of morphine sensitization induced by lateral hypothalamus stimulation in rats

Authors: *Y. RAZAVI[1,2], F. SADEGHZADEH[2], A.-H. PIRASTEH[2], A. HAGHPARAST[2]; [1]Cell. and Mol. Res. Ctr., Tehran, Iran, Islamic Republic of; [2]Neurosci. Res. Ctr., Shahid Beheshti Univ. of Med. Sci., Tehran, Iran, Islamic Republic of

Abstract: Orexin plays a crucial role in drug-seeking behavior. The lateral hypothalamus (LH) is a central region that produces orexin, and its projections to the ventral tegmental area (VTA) play an important role in antinociception. In this study, we investigated the role of LH stimulation and the involvement of the orexin-2 receptor (Ox2r) within the VTA in the development of morphine sensitization on the tail-flick test. In all animals, cannulae were implanted unilaterally into the LH and VTA to inject different doses of carbachol (62.5, 125 and 250 nM/0.5 µl saline) as a cholinergic agonist and TCS (1, 10 and 20 nM/0.3 µl DMSO) as a selective Ox2r receptor antagonist for three consecutive days (sensitization period). These drugs were injected five min before administration of an ineffective dose of morphine (0.5 mg/kg; sc)

during the sensitization period. The five days later, on the test day, tail-flick tests were performed before and after the injection of an ineffective dose of morphine (1 mg/kg; sc), The results revealed that concurrent intra-LH administration of carbachol (250 nmol/0.5 µl saline) and an ineffective dose of morphine (0.5 mg/kg) significantly induce antinociceptive effect. Additionally, the blockade of Ox2r in the VTA by TCS, can attenuate effect of analgesiometer and represented as maximal possible effects (%MPE) induced by concurrent administration of carbachol and an ineffective dose of morphine. Our findings suggest that LH stimulation potentiates the effect of an ineffective dose of morphine, and induces morphine sensitization. It seems that the chemical stimulation of LH potentiates sensitization to morphine through the orexinergic system in the VTA in rats.

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Poster

782. Monoaminergic Plasticity in Addiction

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PhRMA Research Starter Grant

Title: Physical and emotional stress alter voluntary morphine consumption ventral tegmental area gene expression

Authors: S. E. COOPER[1], M. KECHNER[1], *M. S. MAZEI[2];
[1]Neurosci., [2]Physiol., Michigan State Univ., East Lansing, MI

Abstract: There is significant co-morbidity of mood disorders and drug dependence, but the mechanisms contributing to this co-morbidity are not well understood. Preclinical models of mood disorders typically employ chronic stress to elicit depressive-like behaviors. Here, we used physical chronic social defeat stress (CSDS), as well as a modified version, emotional CSDS, to investigate changes in morphine reward and to identify potential molecular mediators of stress susceptibility and reward. We subjected male mice to standard 10-day physical or emotional CSDS and assessed social interaction (SI) on day 11 followed by voluntary morphine consumption using a two-bottle choice assay. Both physical and emotional CSDS decrease SI

score on day 11, with physical stress eliciting more robust social avoidance than emotional stress. Physical and emotional CSDS also significantly increase morphine preference and there is a significant negative correlation between SI score and morphine preference. Given that CSDS induces long-lasting changes in SI, we examined whether changes in morphine reward persist. We observed a similar significant negative correlation between SI score and morphine consumption 14 days after the last defeat. Next, we determined whether morphine preference was also altered during emotional CSDS. Contrary to results following stress, mice undergoing emotional CSDS showed a trend for decreased morphine preference compared to controls. Finally, we wanted to determine whether individual differences in morphine preference could predict susceptibility to CSDS. We found that morphine preference (determined 14 days prior to stress) did not predict susceptibility to CSDS. Combined, these data suggest that CSDS differentially affects morphine reward, depending on when consumption is measured. Given the importance of the ventral tegmental area (VTA) in both CSDS and drug reward, we are currently investigating drug- and CSDS-induced changes in VTA gene expression as potential mediators of these behavioral effects. One promising candidate is serum- and glucocorticoid-regulated kinase 1 (SGK1) as we have found that chronic morphine and physical and emotional CSDS significantly increase SGK1 gene expression in the VTA. We also have preliminary data suggesting that SGK1.1, a brain-specific isoform of SGK1 known to influence neuronal excitability, exhibits a positive correlation with SI score. The decreased expression of SGK1.1 in susceptible mice could contribute to VTA activity changes that influence CSDS susceptibility. Current studies are investigating the role of SGK1, as well as other novel molecules, in drug- and stress-induced changes in the VTA.

Disclosures: **S.E. Cooper:** None. **M. Kechner:** None. **M.S. Mazei:** None.

Poster

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NSERC CGSD

Title: Cannabinoid reward and aversion in the posterior ventral tegmental area is differentially mediated through dopamine projections to the basolateral amygdala or nucleus accumbens shell

Authors: *T. AHMAD[1], S. R. LAVIOLETTE[2];
[1]Dept. of Anat. and Cell Biol., [2]Anat. and Cell Biol., Univ. of Western Ontario, London, ON, Canada

Abstract: The mammalian ventral tegmental area (VTA), is a critical neural region responsible for mediating both rewarding and aversion related behavioural processing and cannabinoids are known to modulate the activity of dopamine (DA) neuronal populations within the VTA. In addition to its well-established DAergic projections to the nucleus accumbens (NAc), the VTA also has functional projections to the prefrontal cortex (PFC) and basolateral amygdala (BLA). Importantly, cannabinoid CB1R transmission strongly modulates the emotional valence of both rewarding and aversive experiences (Ahmad et al., 2013; Laviolette and Grace, 2006). In terms of cannabinoid-related motivational effects, several studies have reported a functional dissociation between the posterior region of the VTA (PVTA), and the anterior region of the VTA (AVTA). For example, cannabinoid receptor activation via THC administration in the PVTA produces rewarding behavioural effects (Zangen et. al., 2006). In contrast, THC was found to have no motivational effects when infused into the AVTA region. Since the PVTA sends DAergic projections to both the BLA and NAc, we wanted to further investigate the possible mechanisms by which cannabinoid reward effects are processed through VTA DAergic outputs. Using an unbiased conditioned place preference (CPP) procedure combined with behavioural pharmacology, we administered either a CB1 agonist (WIN-55,212-2) or antagonist (AM 251) into the PVTA or AVTA of Sprague-Dawley rats. CB1R activation in the PVTA with WIN 55,212-2 (50-500ng) produced a dose-dependent cannabinoid reward CPP, while blockade of CB1R with AM 251 (50-500ng) produced a dose-dependent aversion. Interestingly, when WIN 55,212-2 and AM 251 were micro-infused in the AVTA, no cannabinoid reward or aversion effects were observed. To examine the PVTA-BLA and PVTA-NAc pathways, we used the broad spectrum DA receptor antagonist α-flupenthixol to block DA transmission in either the NAc or BLA. Intra-BLA micro-infusions of α-flu (1μg), blocked the earlier observed cannabinoid reward CPP, but not the cannabinoid antagonist-related aversion. Conversely, intra-NAs micro-infusions of α-flu (1μg), blocked the aversion observed with intra-VTA CB1 antagonist administration, but not the rewarding effects of intra-VTA WIN-55. Thus, our findings demonstrate a functional dissociation between VTA DA outputs to either the NAc or BLA. Furthermore, while the rewarding effects of intra-VTA CB1 activation depend upon a VTA>BLA pathway, the aversive effects of CB1 receptor blockade depend upon VTA DA outputs to the NAc.

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Poster

782. Monoaminergic Plasticity in Addiction

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Title: Stress acutely promotes calcium-dependent glutamatergic synaptic plasticity in the VTA via differential actions of CRF and norepinephrine

Authors: *J. TOVAR-DÍAZ, M. POMRENZE, H. MORIKAWA;
Waggoner Ctr. for Alcohol and Addiction Res., The Univ. of Texas At Austin, Austin, TX

Abstract: Stressful life experiences are a well-known risk factor for the development of addiction. Addiction is driven, in part, by powerful and enduring memories of sensory cues experienced during drug intake. Addictive drugs are thought to hijack synaptic plasticity mechanisms in key brain circuits involved in reward learning, especially the mesolimbic dopaminergic system that originates in the ventral tegmental area (VTA). Glutamatergic inputs activating NMDA receptors (NMDARs) drive dopamine neuron burst firing. Therefore, long-term potentiation of (LTP) of NMDAR-mediated transmission in the VTA may contribute to the increased motivational valence of drug-associated cues. In this study, we tested the hypothesis that stress acutely enhances the induction of NMDAR LTP via rapid, short-term actions of corticotropin-releasing factor (CRF) and norepinephrine (NE), the two key mediators of acute stress responses in the CNS. Mechanistically, LTP induction requires burst-evoked Ca^{2+} signals amplified by preceding activation of the metabotropic glutamate receptor (mGluR)-inositol triphosphate (IP_3) pathway. Using rat VTA slices, we first examined how CRF and NE regulate this Ca^{2+} signal amplification process. We found that bath application of CRF, while having no effect by itself, significantly enhanced facilitation of burst-evoked Ca^{2+} signals caused by direct photolytic application of IP_3 into the cytosol. In contrast, NE or the α_1-adrenergic receptor agonist phenylephrine (Phe), increased burst-evoked Ca^{2+} signals by themselves, as α_1-adrenergic receptors are coupled to IP_3 generation. Furthermore, Phe-induced Ca^{2+} signal facilitation was augmented by co-application of CRF. As a consequence, CRF and Phe differentially promoted NMDAR LTP induction, via facilitation of IP_3 effect and generation of IP_3, respectively, in a cooperative manner. Finally, we found that single and transient exposure to social defeat stress before conditioning resulted in enhanced acquisition of cocaine-conditioned place preference. These results suggest that stress acutely promotes learning of the motivational valence of drug-associated cues via CRF/NE-induced enhancement of glutamatergic synaptic plasticity in the VTA.

Disclosures: J. Tovar-Díaz: None. **M. Pomrenze:** None. **H. Morikawa:** None.

Poster

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PhRMA Foundation Research Starter Grant

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Title: Investigation of biochemical changes induced by chronic morphine and stress in the ventral tegmental area

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Abstract: Drug addiction and depression are two co-morbid diseases that have a significant health and financial burden on society. Increasing evidence suggests that dysfunction of the mesolimbic dopamine (DA) pathway could underlie this co-morbidity. We are investigating the biochemical mechanisms that drive changes in the morphology of ventral tegmental area (VTA) DA neurons induced by chronic morphine and chronic social defeat stress (CSDS). Our previous work demonstrated that exposure to chronic opiates decreases VTA DA neuron soma size in rodents and that this change is dependent on mammalian target of rapamycin complex 2 (TORC2) signaling. Moreover, decreased soma size and TORC2 signaling correlates to changes in opiate reward, highlighting the importance of understanding this process. Preliminary evidence from our lab suggests that mice that are susceptible to CSDS also have a significant decrease in VTA DA soma size. Given these similar alterations in VTA DA soma size, we are seeking to identify the molecular mechanisms. One promising candidate is the Rac1 pathway, which is a well-known mediator of actin cytoskeleton remodeling. Rac1 activity has also recently been linked with TORC2 signaling, as knockout of the TORC2 constituent protein Rictor decreased Rac1 signaling and hippocampal spine density (Huang et al. 2013). Given that chronic morphine decreases TORC2 signaling in the VTA, we are currently determining whether Rac1 activity is also decreased. We have performed western blot analysis on micro-dissected VTA tissue from mice exposed to chronic morphine or CSDS and find a significant decrease in the phosphorylation of cofilin, a protein involved in severing actin filaments, which is downstream of Rac1. We are now examining molecules upstream of cofilin to determine if exposure to

chronic morphine or stress similarly alters activity of these proteins. Additionally, in order to evaluate whether changes in VTA TORC2 signaling are sufficient to alter Rac1 activity, we are conducting western blot analysis of VTA tissue from mice with knockout or viral-mediated overexpression of Rictor. These studies will determine whether decreasing or increasing VTA TORC2 signaling decreases or increases Rac1 signaling, respectively. Thus, the ultimate aim of these studies is to establish the molecular mechanisms underlying VTA DA structural plasticity in the hopes of identifying potential novel targets for therapeutic intervention in drug addiction and depression.

Disclosures: S. Kaska: None. **R. Brunk:** None. **M. Kechner:** None. **M.S. Mazei-Robison:** None.

Poster

782. Monoaminergic Plasticity in Addiction

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIH Grant R01DA039533-01A1

Brain & Behavior Research Foundation (NARSAD) grant

Title: Acute morphine administration induces a partly reversible long term depression of inhibitory synaptic transmission onto dopaminergic ventral tegmental area neurons

Authors: M. E. AUTHEMENT, *F. S. NUGENT;
Pharmacol., Uniformed Services Univ., Bethesda, MD

Abstract: Dopaminergic neurons in the ventral tegmental area (VTA) play an essential role in mediating the acute effects of drugs of abuse. Furthermore, synaptic abnormalities in the VTA following consumption of drugs of abuse likely promote addiction. Our laboratory previously found that a single injection of morphine is sufficient to impair the induction of GABAergic synaptic plasticity onto dopaminergic VTA neurons 24 hours after injection. Here we report that a single morphine injection per se induces a long term depression (LTD) of GABAergic transmission onto dopaminergic VTA neurons. This morphine-induced LTD is present both presynaptically and postsynaptically as evidenced by a decrease in both amplitude and frequency of miniature inhibitory postsynaptic currents (mIPSCs). We then attempted to recover these abnormalities using CL-994, a class I histone deacetylase (HDAC) inhibitor that we recently

demonstrated could recover synaptic abnormalities in the VTA induced by an episode of early life stress. A two hour incubation of rat midbrain slices in Cl-994 managed to recover mIPSC amplitudes to normal levels. These results suggest that the acute effects of morphine administration may in part be mediated by epigenetic mechanisms, namely histone deacetylation.

Disclosures: M.E. Authement: None. **F.S. Nugent:** None.

Poster

782. Monoaminergic Plasticity in Addiction

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 782.18/K1

Topic: C.17. Drugs of Abuse and Addiction

Support: CIHR 404233

Title: Blockade of connexin-36-expressing gap junctions in the ventral tegmental area prevents opiate withdrawal aversions in opiate-dependent animals

Authors: *G. MAAL-BARED, M. PATEL, M. CHWALEK, D. VAN DER KOOY;
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Abstract: The ventral tegmental area (VTA) is crucial for reward seeking and seems to promote both adaptive and maladaptive behaviors such as foraging and drug seeking. The animal's prior exposure to the substance dictates which VTA efferents mediate the behavior. Descending projections to the tegmental pedunculopontine nucleus (TPP) are necessary for morphine conditioned place preferences (mCPP) in opiate-naïve but not opiate-dependent animals, whereas ascending mesoaccumbal dopamine (DA) outputs are necessary for mCPP in dependent but not naïve animals. This switch in neural substrates is due to changes in the conductance of GABAA receptors on VTA GABA neurons that renders half the GABA neurons hyperexcitable to GABAA agonists. Preliminary evidence suggests this is due to increased intracellular chloride concentrations and, subsequently, chloride efflux and depolarization upon GABAA activation. A possible mechanism by which this occurs is the downregulation of the potassium chloride cotransporter, KCC2, which normally expels chloride ions from the cell. VTA infusions of a KCC2 blocker promote the aforementioned GABA changes and also cause a switch in the substrate underlying mCPP such that the naïve reward is mediated by accumbal DA activity, suggesting that inverted chloride gradients are important for the switch to an opiate-dependent state. VTA GABA cells form a network of electrically-coupled cells that fire synchronously. This pattern of activity is mediated by connexin-36 (Cx36)-expressing gap junctions, which

permit rapid ion transfer between cells. Given that corticotegmental glutamate enhances Cx36 coupling and KCC2 downregulation, we hypothesized that electrical synaptic communication within the GABA population may contribute to the switch to an opiate-dependent state. Indeed, we found that Cx36 blockade reverts opiate-dependent rats to a TPP-dependent, naïve-like state. Furthermore, dependent rats did not avoid a withdrawal-paired compartment when conditioning sessions were preceded by VTA infusions of the Cx36 blocker, mefloquine. By contrast, these rats still exhibited somatic withdrawal signs such as tremors, head-shakes and scratches despite mefloquine administration. These experiments strongly suggest that Cx36-expressing gap junctions are necessary for both the switch to an opiate-dependent state as well as the experience of withdrawal aversions. Due to the non-specific effects of mefloquine, we currently are utilizing mice with a floxed Cx36 gene to verify that the switch in the neural substrate mediating mCPP and the block of opiate-withdrawal aversions are due to Cx36 blockade rather than other effects of the drug.

Disclosures: G. Maal-Bared: None. **M. Patel:** None. **M. Chwalek:** None. **D. van der Kooy:** None.

Poster

783. Adolescence and Addiction

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 783.01/K2

Topic: C.17. Drugs of Abuse and Addiction

Title: Failure of nicotine exposure during the peripubertal period to induce sensitization to the administration of cocaine to the adult female rat

Authors: B. A. MCMILLEN[1], C. T. PERRY[2], G. R. WOODS[2], H. L. WILLIAMS[1], *D. A. TAYLOR[1];
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Abstract: There is strong concern that the use of nicotine, either as tobacco or electronic cigarettes, early in adolescence may lead to later use of other drugs of abuse by the adult. Administration of nicotine, 0.4 mg/kg i.p. as the base, to male rats from postnatal days (PD) 35 - 44 results in adults that show enhanced reward like responses to nicotine itself, cocaine and diazepam when testing begins at PD 80 (Adriani et al, J Neurosci 2003; McMillen et al, Eur J Pharmacol 2005; James-Walke et al Neurotox Teratol 2007). The nicotine exposure also caused a long-term increase in the expression of Fos-B that forms an important gene regulatory protein. These studies and several others were all done with male rats or male mice as subjects. An

important issue is whether or not the same phenomenon can be demonstrated in female rodents. 36 female Sprague-Dawley rats were purchased from Charles River Labs for this study and housed under standard conditions in pairs. Beginning on PD 35, tails were marked, the animals weighed and 0.4 mg/kg nicotine hydrogen tartrate (dose as free base) or 0.9% saline injected i.p. for 10 days. Beginning on PD 80, the rats were put into a conditioned place preference (CPP) apparatus for 15 min: days 1, 2, and 3--free exploration; days 4, 6, 8, 10--injection of vehicle or drug and confinement to the least preferred side; days 5, 7, 9, 11--injection of saline and confinement to the preferred side; day 12_free exploration. On days 3 and 12, the movement of the rats was observed with the total number of chamber entries (frequency as a measure of overall activity) and the time spent on each side of the apparatus recorded (as a measure of the reward effect). The frequency of entries for the vehicle-exposed/vehicle-treated rats was 38 ±13. Neither exposure to nicotine nor treatment with 0, 1.0 or 3.0 cocaine-HCl (dose as the base and dissolved in citrate buffer) altered the overall activity of the rats. The change in time spent on the least preferred side did not show a significant effect by 3-way ANOVA, $F(2,2,31) = 2.35$, $p > 0.05$. The only group to show a significant change from pre-treatment to post-treatment by a paired t-test was for the nicotine-exposed/3.0 cocaine group, 220 ±22 to 340 ±32 seconds. However, this change was not different from the corresponding vehicle-exposed group. These data suggest that the female rat does not exhibit a peripubetal nicotine-induced heterologous sensitization to drugs of abuse as reported repeatedly to occur with the male rat. (CTP and GRW were participants in the High School Medical Research Program of Pitt County Schools)

Disclosures: B.A. McMillen: None. **C.T. Perry:** None. **G.R. Woods:** None. **H.L. Williams:** None. **D.A. Taylor:** None.

Poster

783. Adolescence and Addiction

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Program#/Poster#: 783.02/K3

Topic: C.17. Drugs of Abuse and Addiction

Title: Inhibition of nicotine-induced expression of ΔFosB in the molecular cell layer of the hippocampus dentate gyrus by minocycline in the peripubertal rat

Authors: P. S. NAGCHOWDHURI[1], K. T. LANE[2], *B. A. MCMILLEN[1];
[1]Pharmacol & Toxicol, [2]Pharmacol. & Toxicology, East Carolina Univ., Greenville, NC

Abstract: Nicotine use during adolescence is considered to be a ‘gateway’ that leads to the brain’s sensitization to other illicit substances in the future. Psychoactive drugs such as nicotine

are known to induce the expression of the transcription factor ΔFosB that facilitates this sensitization process. A previous study from our laboratory showed that a once daily, 10-day administration of nicotine that bracketed the onset of puberty in male rats, postnatal days (PD) 35 - 44, at an intraperitoneal (i.p.) dose of 0.4 mg/kg induced the expression of ΔFosB in selected memory and reward subset areas of the rat brain. Further this expression persisted into adulthood (PND 80), especially in the nucleus accumbens (NAc) and dentate gyrus of hippocampus (DG) (Soderstrom et al. Psychopharmacol 2007). Our long-term goal is to extend the previous study by elucidating the role of microglia in this sensitization process *in vivo*. Our hypothesis is that there is a linkage between microglia activation and ΔFosB induction. In this study, minocycline, a lipophilic tetracycline antibiotic commonly used to suppress the activation of microglia *in vivo*, was injected into periadolescent male Sprague Dawley (SD) rats prior to nicotine administration to assess the impact of microglia activation on ΔFosB induction by nicotine. Male rats received once daily injections from PD 35 - 44 and were divided into four treatment groups: Vehicle, 0.4 mg/kg nicotine; 30 mg/kg minocycline and minocycline 30 min before nicotine. Similar to the report by Soderstrom and colleagues, 0.4 mg/kg i.p. of nicotine-bitartrate (all drugs dosed as free base) once daily from PD 35 - 44 increased the density ΔFosB immuno-labeled neuronal neuclei in the DG from the control by 39% ($F_{3,9} = 6.94$, $p=0.01$; Dunnett's t-test $p < 0.05$). Minocycline-HCl pretreatment 30 minutes prior to each dose of nicotine at a dose of 30 mg/kg i.p. changed the density of ΔFosB labeled nuclei by 24% compared to control and was not significantly different from control ($p>0.05$, Dunnett's t-test). The nicotine treatment group appeared to have fewer ramified microglia (non-activated) than did either the control or minocycline plus nicotine groups although this result did not reach significance due to the small number of animals ($N = 3$ per cell, $F_{3,8} = 0.881$). Thus, minocycline pre-treatment reduces the ability of nicotine to increase the expression of ΔFosB in the DG and may be due to the reduction in microglial activation produced by this drug. This study will further analyze the effect of minocycline on ΔFosB induction in the NAc, prefrontal cortex (PFC), and the ventral tegmental area (VTA).

Disclosures: **P.S. Nagchowdhuri:** None. **K.T. Lane:** None. **B.A. McMillen:** None.

Poster

783. Adolescence and Addiction

Location: Hall A

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Program#/Poster#: 783.03/K4

Topic: C.17. Drugs of Abuse and Addiction

Support: Ronald McNair Foundation

Title: An analysis of the interaction of methylphenidate and nicotine in adolescent rats: Effects on BDNF

Authors: *E. D. CUMMINS, K. K. LEEDY, D. J. PETERSON, S. K. KIRBY, L. J. HERNANDEZ, R. W. BROWN;
East TN State Univ., Johnson City, TN

Abstract: This study was designed to analyze the interaction of adolescent exposure to methylphenidate (MPH; trade name: Ritalin) on nicotine sensitization and conditioned place preference (CPP) in rats. MPH is the most commonly prescribed medication for Attention Deficit-Hyperactivity Disorder (ADHD) which is diagnosed in 3-5% of adolescents in the United States. There are several studies that have shown adolescent MPH exposure may alter plasticity of the brain's dopamine reward system and cause an increased susceptibility to drug abuse. In the present study, rats were treated ip with 1 mg/kg MPH or saline using a "school day" regimen of five days on, two days off, from postnatal day (P)28-50. A 1 mg/kg dose of MPH has been shown to result in brain plasma levels equivalent to clinical dosing in humans. During the final two weeks of MPH treatment, animals were either behaviorally sensitized to nicotine (0.5 mg/kg free base) or saline for 12 days, or conditioned to nicotine or saline using the CPP behavioral paradigm. Behavioral sensitization is a test of the activating effects of drugs which is typically mediated by the brain's dopamine system. CPP is a test of the associative value of rewarding drugs. In addition, three days after behavioral sensitization was complete, animals were analyzed for stress behavior using the forced swim stress behavioral test. During behavioral sensitization and CPP, MPH was always given in the morning, whereas behavioral testing with nicotine was performed later in the day. For forced swim stress, animals were tested in a drug free state. Animals were tested with nicotine 6 h after MPH treatment, equivalent of six drug half lives because the half life of MPH is 1 h. For sensitization, animals were treated with either nicotine or saline 10 min before placement into a square locomotor arena (30 cm/side) and activity measured. For CPP, a pre-test was given to determine preference in a three chamber shuttle box, and animals were always conditioned with nicotine against their natural preference. Behavioral results revealed that adolescent pre-exposure to MPH reduced nicotine behavioral sensitization in female but not male rats during the first week of testing. However, MPH enhanced nicotine CPP in both adolescent male and female rats. Interesting, animals administered MPH demonstrated a significantly decreased latency to immobility in the forced swim stress behavioral test. Brain tissue was taken after CPP and will be analyzed for Brain-derived neurotrophic factor (BDNF), which is known to play a critical role in synaptic maintenance and growth. Implications towards the influence of MPH on nicotine use and its application will be discussed.

Disclosures: E.D. Cummins: None. **K.K. Leedy:** None. **D.J. Peterson:** None. **S.K. Kirby:** None. **L.J. Hernandez:** None. **R.W. Brown:** None.

Poster

783. Adolescence and Addiction

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 783.04/K5

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIDA R01-DA-027222

Title: Locus coeruleus neuronal firing directly correlates with behavioral response to acute and chronic doses of methylphenidate (ritalin) in adolescent rats

Authors: N. KHARAS[1], C. REYES-VASQUEZ[2], *J. ARONOWSKI[3], N. DAFNY[1];
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[2]Departmento de Fisiologia, Univ. Nacional Autonoma de Mexico, Mexico City, Mexico;
[3]Neurol., Univ. Texas HSC - Houston, Houston, TX

Abstract: Attention deficit hyperactivity disorder (ADHD) is the most common disorder diagnosed in adolescents (ages 8-15) in the United States. ADHD is a behavioral disorder characterized by increased inattention, hyperactivity, and impulsivity. Currently, Methylphenidate (MPD), also known as Ritalin, is the most effective method to treat adolescents with ADHD. The objective of this study is to evaluate the behavioral and neuronal changes induced by acute and chronic MPD administration. Specifically, there is a lack of knowledge of the changes in norepinephrine (NE) in response to MPD. Thus neuronal firing was recorded from locus coeruleus (LC), the main site of NE synthesis in the CNS, while simultaneously observing locomotor activity in freely moving adolescent rats. Adolescent rats were chosen to mimic the age group correlate in humans most affected by the disease. Also, in light of personalized medicine each rat was evaluated individually in addition to studying them as a group. Following acute dose of MPD, all rats showed an increase in locomotor activity and increase in LC neuronal firing. However, upon the chronic dose of MPD, individual rats either showed an increase or decrease in their locomotor and LC neuronal activity as compared to the acute dose in a dose dependent manner; these rats were labeled as sensitized and tolerant respectively. Neuronal firing in LC directly corresponded with the changes observed in behavioral locomotor activity. This study shows the role of LC in acute and chronic doses of MPD. Furthermore, the study indicates that there is a relationship between the LC neuronal responses and behavioral expression upon exposure to MPD. Neuroadaptations of sensitization or tolerance have shown to be key factors in drug response, dependence and addiction. Observing individual rodents and being able to predict their neuroadaptation to psychostimulant drugs such as MPD could

eventually create a platform for predicting the sensitivity and likelihood of abuse in individual patients allowing for tailored treatments and application in the future of personalized medicine.

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Poster

783. Adolescence and Addiction

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 783.05/K6

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH Grant ROI DA027222

Title: Methylphenidate modulates dorsal raphe neuronal activity: behavioral and neuronal recordings from adolescent rats

Authors: H. WHITT[1], C. REYES-VASQUEZ[2], N. KHARAS[1], *N. DAFNY[1];
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Abstract: Methylphenidate (MPD) is one of the most widely prescribed psychostimulants for the treatment of attention deficit hyperactive disorder (ADHD) in children and adults. MPD binds to presynaptic catecholamine transporters in the CNS and prevents reuptake of norepinephrine and dopamine from the synaptic cleft. Unlike the psychostimulants cocaine and amphetamine, MPD does not exhibit direct actions on the serotonin transporter. Studies investigating MPD tend to focus on its effects on the CNS dopamine circuit, however there is evidence suggesting that MPD affects the serotonergic system as well. This study aimed to investigate the role of the dorsal raphe, a major source of serotonergic innervation in the mammalian brain, in the response to acute and chronic MPD exposure. The hypothesis of the study is 1) the dorsal raphe (DR) participates in MPD action, 2) the same chronic MPD dose in some adolescent animals will elicit behavioral sensitization and in others behavioral tolerance and 3) the DR neuronal activity recorded from adolescent animals expressing behavioral sensitization to chronic MPD will have a significantly different response to MPD exposure than those DR neurons recorded from animals expressing behavioral tolerance to chronic MPD. Freely behaving animals previously implanted bilaterally with permanent electrodes were used. Behavioral and DR electrophysiological activity were concomitantly recorded following acute and chronic MPD exposure using an open field assay and a wireless recording system over 10 experimental days.

Four groups of animals were used: one control group (saline) and three experimental groups treated with 0.6, 2.5, and 10.0 mg/kg MPD respectively. The animals received daily MPD or saline injections on experimental days 1-6, followed by 3 washout days and MPD rechallenge dose on experimental day (ED)10. The same chronic dose of MPD resulted in either behavioral sensitization or tolerance. DR neurons responded to acute MPD in a dose dependent manner. Neuronal activity recorded from the DR units of rats expressing behavioral sensitization to chronic MPD exposure exhibited a significantly ($p < .05$) different response to MPD rechallenge on ED10 compared to the DR neuronal activity recorded from animals that expressed behavioral tolerance to chronic MPD. This correlation between behavioral response and DR neuronal activity following chronic MPD exposure indicates that the DR is involved at least in part in the acute effects of MPD as well as the chronic effects of MPD (expression of sensitization and tolerance) in adolescent rats. The study confirms our hypothesis.

Disclosures: **H. Whitt:** None. **C. Reyes-Vasquez:** None. **N. Kharas:** None. **N. Dafny:** None.

Poster

783. Adolescence and Addiction

Location: Hall A

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Program#/Poster#: 783.06/K7

Topic: C.17. Drugs of Abuse and Addiction

Support: NIH Grant ROI DA027222

Title: Medial prefrontal cortex electrophysiological and behavioral recordings following acute and chronic methylphenidate exposure in freely behaving adolescent SD rats

Authors: C. CLAUSSEN[1], C. CANNON[1], *P. DASH[2], N. DAFNY[1];
[1]Univ. of Texas Med. Sch., Houston, TX; [2]Univ. Texas Med. Sch., Houston, TX

Abstract: Methylphenidate (MPD), a drug often prescribed for the treatment of attention-deficit hyperactivity disorder, has a potential for abuse and misuse. The prefrontal cortex is one of many areas of the brain that responds to MPD. Most of the MPD studies have been completed in adult subjects while most of the users were adolescent. The objective of this study is to investigate the acute and chronic dose response characteristics of MPD on prefrontal cortex (PFC) neuronal activity recorded in freely behaving adolescent rats. The experiment lasted for 10 consecutive days after the recovery from implanting 4 permanent semi microelectrodes in the PFC. Four groups of animals were used: saline (control), 0.6, 2.5, and 10 mg/kg MPD groups. On experimental day 1 (ED1), baseline recording (concomitant neuronal and behavioral) was

obtained following either a saline (control), 0.6, 2.5, or 10 mg/kg MPD doses. On ED2 to ED6 each group was injected with their assigned dose (saline, 0.6, 2.5, or 10 mg/kg MPD). ED7 to ED9 were washout days. On ED10, behavioral and neuronal recordings were resumed as on ED1 following saline and MPD exposure. Acute MPD was found to elicit a dose response increase of animals' locomotor activity. Rechallenge with MPD at ED10 compared to the effect of MPD at ED1 showed no significant differences. When the animals were divided into two groups based on their individual responses to chronic MPD exposure, some animals expressed behavioral tolerance and others sensitization to all three MPD groups. Electrophysiologically, a dose response characteristic for acute and chronic MPD exposure was observed. With increasing MPD doses, more PFC units responded by changing their firing rate from 36%, 63%, and 78% PFC units responded for the acute MPD exposure at ED1 to 48%, 69%, and 82% of the units following chronic exposure at ED10 to 0.6, 2.5, and 10.0 mg/kg MPD, respectively. The neuronal responses to MPD recorded from animals expressing behavioral tolerance were significantly different compared to the neuronal population responses recorded from animals expressing behavioral sensitization to repetitive MPD exposure. The majority of the PFC units recorded from animals expressing behavioral tolerance responded to the drug predominately by decreasing their firing rates, whereas those PFC units recorded from the behaviorally sensitized animals mainly showed an increase in their firing rates. The possible mechanisms are discussed.

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Poster

783. Adolescence and Addiction

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: C.17. Drugs of Abuse and Addiction

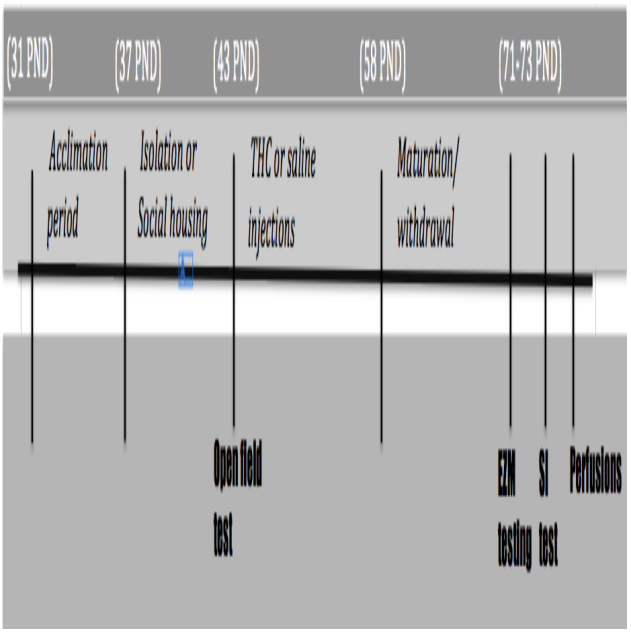
Support: Internal grant, Nipissing University

Title: Chronic adolescent exposure to THC and induced anxiety changes behaviour in adult rats

Authors: ***A. C. WEEKS**, M. BOUDREAULT, K. NORRIS, J. ANDREWS, N. LANDRY, C. LALONDE, B. WEEGAR, A. STILLAR, M. J. SAARI;
Nipissing Univ., North Bay, ON, ON, Canada

Abstract: The legalization and increased use of cannabis and its main constituent Δ9-tetrahydrocannabinol (THC), as a recreational and medicinal drug, has enhanced research interest related to the potential interactions of cannabis use and other psychological conditions.

For example, adults and adolescents often report using cannabis as a way of coping with stress and anxiety. While the effects of marijuana use on the adult brain are fairly well understood, less is known about chronic use during adolescence. This study assessed anxiety levels and social interaction after an isolation stressor event and chronic adolescent phase injections of THC in rats. Four experimental groups included: isolation/THC, no isolation/THC, isolation/vehicle, and no isolation/vehicle. Following one week in the housing condition (isolation or social housing), daily THC or vehicle injections were carried out for 15 days starting at post-natal day 43 (see Fig. 1). An open field test was completed after the isolation period, but before injections, to assess initial anxiety levels. Following the injections, a withdrawal period, and a maturation delay, an elevated zero maze and a social interaction task were used to assess anxiety related behavioural changes. The behavioural results from the zero maze indicated that chronic adolescent THC administration following isolation-induced stress caused adult rats to spend less time in the closed regions during the first minute in the maze. For the social interaction task, there was a main effect of the drug where animals treated with THC were found to groom other rats significantly less often. These results suggest that using cannabis during adolescence changes the response to anxiety provoking situations. Following the behavioural tests, the rats were perfused for confocal microscopy. Pilot data from this analysis related to changes in synaptic protein levels in the amygdalar subregions of these animals will be presented. Figure 1



Disclosures: **A.C. Weeks:** None. **M. Boudreault:** None. **K. Norris:** None. **J. Andrews:** None. **N. Landry:** None. **C. Lalonde:** None. **B. Weegar:** None. **A. Stillar:** None. **M.J. Saari:** None.

Poster

783. Adolescence and Addiction

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIMH Grant R01 MH100228

Title: Adolescent cannabinoid administration causes oxidative stress

Authors: *S. MUKHERJEE[1], T. HWANG[2], S. PAWAR[3], A. AROUMOUGAME[3], S. GHOSE[1];
[1]Dept. of Psychiatry, [2]Dept. of Clin. Sci., [3]Dept. of Radiation Oncology, UT Southwestern Med. Ctr., Dallas, TX

Abstract: Adolescent cannabis use (ACU) is an environmental risk factor repeatedly implicated in the pathophysiology of schizophrenia. The mechanism by which ACU might predispose the brain to schizophrenia is unknown. One plausible hypothesis is that the use of cannabis during a period of brain maturation leads to persistent neural changes that lead to the development of schizophrenia. Further, there is evidence that individuals with schizophrenia and a history of ACU (S-ACU+) compared to schizophrenia without a history of ACU (S-ACU-) exhibit distinct clinical profile in terms of onset of illness, severity of psychosis and cognitive function. Based on our preliminary cell culture studies demonstrating that acute administration of cannabinoid agonists induce oxidative stress, we hypothesized that ACU induces oxidative stress in the developing brain to predispose to schizophrenia. To investigate this hypothesis, we assembled a human post mortem cohort of DLPFC (BA 9) tissue from cases of schizophrenia and matched controls, each divided into those with and without ACU (n=10 per group). Whole transcriptome sequencing of DLPFC region was conducted in these cases. Our preliminary analyses reveal significant differences in oxidative stress pathways between the two schizophrenia groups. RT-PCR analyses of selected genes in this pathway recapitulated transcriptome sequencing results. Further bioinformatic analyses and molecular characterization of DLPFC at the mRNA and protein level and cellular localization studies of gene expression changes are ongoing.

Disclosures: S. Mukherjee: None. **T. Hwang:** None. **S. Pawar:** None. **A. Aroumougame:** None. **S. Ghose:** None.

Poster

783. Adolescence and Addiction

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Topic: C.17. Drugs of Abuse and Addiction

Support: K01DA071345

Pennsylvania Department of Health

Title: Determining the ontogeny of working memory, and the effects of cannabinoid self-administration, in adolescent rats

Authors: *E. K. KIRSCHMANN, M. W. POLLOCK, V. NAGARAJAN, M. M. TORREGROSSA;
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Abstract: Adolescence is characterized by risky behaviors like drug-taking, and marijuana (Cannabis sativa) use is widespread. Importantly, the neurobiological consequences of chronic cannabis use are not yet well-known. Adolescence is a period of neurodevelopment in the prefrontal cortex (PFC), a key regulator of cognition and inhibitory control, and thus there is potential for adolescent cannabis use to cause long-term effects on cognitive function. Though some rodent and primate research has shown evidence of cognitive deficits after experimenter-administered cannabinoids during adolescence, it remains unknown whether similar deficits occur in a model of drug use and addiction - cannabinoid self-administration. In order to understand what effects cannabinoid self-administration has on cognition, we first identified the critical period for the ontogeny of working memory performance in adolescents. We then established intravenous self-administration of the synthetic cannabinoid agonist WIN55,212-2 (WIN) in a short-access (2hr) paradigm in male rats and examined the long-term effects of cannabinoid self-administration during adolescence on working memory performance. Adolescent (starting on postnatal day 28; p28; n=12) and adult (>p70; n=8) male rats were trained on a delayed-match-to-sample working memory task, and performance was compared daily. Adolescent performance in the working memory task was consistently worse than adults at long delays up to p46, and did not reliably overlap adult performance until late adolescence (p51). Accurate performance on the task was dependent on activity in the prelimbic PFC in adults. Separate groups of rats were trained to self-administer WIN (n=12) or sucrose (controls; n=11) in daily 2-hr sessions during adolescence (p38-49). Working memory training began in adulthood (p87-94), and testing continued daily until p118. Short-access WIN self-administration during adolescence did not substantially impair working memory performance in adulthood. Taken together, our findings suggest that working memory becomes adult-like in late-adolescence; and adolescent short-access cannabinoid self-administration does not cause

substantial impairments in long-term cognitive function. Ongoing studies will determine whether: 1) developmental changes in GABAergic signaling are associated with developmental improvements in working memory, and 2) long-access (6hr) WIN self-administration during adolescence impairs working memory.

Disclosures: E.K. Kirschmann: None. **M.W. Pollock:** None. **V. Nagarajan:** None. **M.M. Torregrossa:** None.

Poster

783. Adolescence and Addiction

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 783.10/K11

Topic: C.17. Drugs of Abuse and Addiction

Support: NIH Grant DA027683

Title: Chronic nicotine exposure during adolescence alters the rewarding properties of the cannabinoid agonist CP 55,940 in young adult male rats

Authors: A. D. HARDIN, M. J. STONE, Z. R. HARMONY, G. J. KAPLAN, *C. A. CRAWFORD;
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Abstract: Adolescent exposure to nicotine alters the behavioral response to a number of addictive drugs in rodents. Specifically, adolescent nicotine treatment potentiates the reinforcing value of both cocaine and alcohol, and decreases the aversive properties of cocaine. More recently, a number of studies have demonstrated that adolescent exposure to nicotine alters the functioning of cannabinoid systems. For example, adolescent nicotine treatment enhances the unconditioned response to cannabinoid agonists, and increases the density of cannabinoid receptors. Whether chronic nicotine exposure starting in adolescence alters the rewarding properties of cannabinoid agonists (e.g., CP 55,940) has not been determined. To this end, we exposed rats to nicotine from early adolescence until adulthood and then assessed CP 55,940-induced conditioned place preference (CPP). Male Sprague-Dawley rats were given daily nicotine injections (0, 0.16, 0.32, or 0.64 mg/kg, sc) starting on postnatal day (PD) 31 and continuing for 42 consecutive days (i.e., throughout the course of the experiment). On PD 60, cannabinoid-induced CPP was assessed using a 10-day biased procedure, consisting of 1 preconditioning day, 10 conditioning days, and 1 test day. Rats were pre-exposed to CP 55,940 (0, 10, 20, or 30 μg/kg, ip) on the preconditioning day. During the conditioning phase, rats

received alternating daily treatments of saline or the same dose of CP 55,940 (0, 10, 20, or 30 μg/kg) that was administered on the preconditioning day. Among saline-pretreated rats, only 30 μg/kg CP 55,940 was able to induce CPP. In contrast, rats pretreated with 0.32 mg/kg nicotine exhibited a statistically significant CPP when a substantially lower dose of CP 55,940 (10 μg/kg) was used. These findings suggest that exposure to nicotine during adolescence enhances the rewarding value of a low dose of a cannabinoid agonist.

Disclosures: A.D. Hardin: None. **M.J. Stone:** None. **Z.R. Harmony:** None. **G.J. Kaplan:** None. **C.A. Crawford:** None.

Poster

783. Adolescence and Addiction

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIH Grant RO1 DA025674

NIH Grant RO3 DA034886

Title: Female adolescent morphine exposure causes transgenerational effects on metabolism

Authors: *F. M. VASSOLER, C. WYSE, A. KUBEREK, K. HUYNH, G. WIDMER, E. M. BYRNES;
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Abstract: Opiate use is a growing epidemic affecting young populations. Utilizing a rodent model, we have observed changes in gene expression related to metabolism within hypothalamic nuclei in offspring of females exposed to morphine during adolescence. These findings indicate that adolescent exposure to morphine may cause transgenerational effects on metabolism. Additionally, there is a reported connection between opiate exposure and increased intake of high sucrose foods. Therefore, we hypothesize that disruption of the endogenous opioid system during a critical developmental period might cause long term changes in metabolism that extend into future generations. To test this, morphine was administered to female Sprague Dawley rats for 10 days during adolescence (P30-P39) using an increasing dosing regimen (5-25 mg/kg, s.c.). Control animals received matched saline injections. Then, animals remained in their home cage, drug free, until adulthood (after P60) at which point they were introduced to drug-naïve colony males. The offspring (F1 animals) were placed on one of three diets at P30: control, high fat, or

high sucrose. The animals remained on the diet for 40 days and were weighed weekly. On P70 fasting glucose levels were measured. Fecal samples were collected just prior to being placed on the new diets and following 6 weeks on the diet for microbiota DNA sequencing. We found that among the male offspring, there was a main effect of maternal opiate history on weight gain with Mor-F1 animals gaining significantly more weight than Sal-F1 animals. Post hoc analyses revealed that there was a significant increase in weight gain in Mor-F1 animals on the high fat diet. There was no significant effect in female offspring. However, there was a trend towards an increase in weight gain in the Mor-F1 females compared to the Sal-F1 females fed a high sucrose diet. Analysis of fasting glucose levels revealed a main effect of maternal opiate history in the male offspring with significantly increased blood glucose levels in Mor-F1 males following a high fat diet as well as a high sucrose diet. While there was no significant effect in females, there was a trend observed again in the high sucrose diet of increased fasting glucose levels in Mor-F1 females. Analysis of the microbiome is ongoing. The data provide evidence of a shift in metabolic functioning in offspring of females exposed to morphine during adolescence. The direction of the shift indicates the possibility that Mor-F1 animals have an increased propensity towards metabolic syndrome.

Disclosures: **F.M. Vassoler:** None. **C. Wyse:** None. **A. Kuberek:** None. **K. Huynh:** None. **G. Widmer:** None. **E.M. Byrnes:** None.

Poster

783. Adolescence and Addiction

Location: Hall A

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Program#/Poster#: 783.12/K13

Topic: C.17. Drugs of Abuse and Addiction

Support: Program to Enhance Scholarly and Creative Activities (PESCA)

Title: Contribution of MRGPRB4-expressing sensory neurons to the socio-environmental effect on opioid dependence and reward in adolescent mice

Authors: M. BATES, M. A. EMERY, P. J. WELLMAN, *S. EITAN;
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Abstract: Drug abuse is strongly influenced by socio-environmental factors. Social support (or lack thereof) is reported as a factor that may affect the propensity to escalate from episodic use of opioids to dependence and abuse. Our recent studies demonstrated that social environment

(i.e., housing conditions) influence the development of morphine dependence and reward in adolescent mice. More specifically, our previous studies show that being housed with drug-naïve animals has a protective effect on the severity of somatic withdrawal symptoms upon cessation of drug administration, as well as the likelihood of developing, and maintaining, morphine reward. However, the physiological mechanisms of this effect are unknown. Thus, the objective of this study was to advance our understanding of the mechanisms mediating the socio-environmental effect on the development of morphine dependence and reward. Massage-like stroking (grooming) is a form of supportive social interaction in rodents. This supportive social interaction was recently suggested to be, at least partially, mediated by peripheral dorsal root ganglia sensory neurons expressing the G-protein coupled receptor MRGPRB4. It was shown that pharmacogenetic activation of MRGPRB4+ neurons induces conditioned place preference in adolescent mice, indicating that this activation is reinforcing. Because social grooming in mice may act as a form of social support, we chose to examine if pharmacogenetic manipulation of the sensation resulting from grooming is mediating the social housing effect on morphine dependence and reward. In this study, we used DREADD technology to activate/silence sensory MRGPRB4-expressing neurons in awake, freely moving animals. This was done in order to stimulate or block the 'sensation of social support' from social grooming. We tested how manipulating the activity of sensory MRGPRB4-expressing neurons affected the development of morphine dependence and reward in animals housed in different social environments (i.e., housed with drug-naïve animals vs. housed only with morphine-treated animals). We found that MRGPRB4-expressing neurons are involved in mediating the environmental (housing) effect on the severity of somatic withdrawal symptoms upon cessation of drug administration. These results suggest that sensation of social support, resulting from massage-like stroking and activation of MRGPRB4-expressing neurons, alters the development of morphine dependence in adolescents.

Disclosures: **M. Bates:** None. **M.A. Emery:** None. **P.J. Wellman:** A. Employment/Salary (full or part-time):; Texas A&M Univ. **S. Eitan:** A. Employment/Salary (full or part-time):; Texas A&M Univ.

Poster

783. Adolescence and Addiction

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 783.13/K14

Topic: C.17. Drugs of Abuse and Addiction

Title: Differences between adult and adolescent rats in locomotor sensitization to codeine

Authors: *T. ZAFAR, A. ESCOBEDO, V. ESPINOZA, A. ROCHA, K. TRUJILLO;
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Abstract: Codeine (COD) is an opioid analgesic that acts predominantly via interaction with μ-opioid receptors. Codeine mixtures sometimes referred to as "sizzurp" or "purple drank," have been increasingly abused in the hip-hop culture. Moreover, because of its broad availability, COD is often used by teens for recreational purposes. Evidence suggests that abuse of COD can lead to compulsive use and abuse. Behavioral sensitization is an increase in an effect of a drug after repeated administration. Also referred to as "reverse tolerance," sensitization is thought to be involved in the development of addiction. While there are reports of behavioral sensitization to opioids in adult rats, little has been done to elucidate sensitization in adolescents, and potential differences in sensitization between adults and adolescents. The present study examined the locomotor effects of COD following repeated administration to adolescent and adult Sprague-Dawley rats. We hypothesized that COD would induce an increase in locomotor activity across days reflective of behavioral sensitization and that adolescent rats would differ in sensitization when compared to adults. Animals received saline or COD (10 mg/kg s.c.), once daily for seven (7) days and locomotor activity was assessed each day. COD produced very little change in locomotor activity on day 1, however, activity escalated across days of treatment, reflecting the development of sensitization. Furthermore, although there were only modest differences between adolescents and adults early in treatment, there was evidence of greater sensitization in adolescents. Thus, while repeat administration of COD leads to behavioral sensitization, we found that this sensitization differs in adults and adolescents. Further research will help to determine the factors involved in COD sensitization in adults and adolescents, and may lead to better prevention and treatment for COD abuse and addiction in teenagers.

Disclosures: T. Zafar: None. **A. Escobedo:** None. **V. Espinoza:** None. **A. Rocha:** None. **K. Trujillo:** None.

Poster

783. Adolescence and Addiction

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Program#/Poster#: 783.14/K15

Topic: C.17. Drugs of Abuse and Addiction

Support: GM-08807

Title: Differences in ketamine-induced ultrasonic vocalizations in adult and adolescent rats: the balance between reward and aversion

Authors: *R. M. ALTAMIRANO, T. T. TOWNER, A. ESCOBEDO, K. A. TRUJILLO; California State Univ. San Marcos, San Marcos, CA

Abstract: Ketamine (KET) is a dissociative anesthetic and non-competitive NMDA receptor antagonist. Sometimes referred to as 'Special K' or 'K', KET is used at subanesthetic doses at dance clubs and raves and therefore falls into the diverse class known as club drugs. KET produces pleasurable effects in many users, but has also been reported to produce unpleasant responses in some users, including an intense dissociative response known as the 'K-Hole', which is often reported as disturbing or frightening. Although adults and teenagers have increasingly abused ketamine, little is known about differences in response at different ages. The current study examined Ultrasonic Vocalizations (USVs) in adult and adolescent Sprague-Dawley rats following administration of KET. USVs are high frequency calls made by rodents that have been found to reflect affective responses. High frequency 50 kHz USVs, are associated with pleasurable stimuli or positive affect and lower frequency 22 kHz USVs are associated with aversive stimuli or negative affect. By quantifying the number of 50 kHz and 22 kHz calls, the affective response to KET can be determined. Adolescent rats received saline or KET (30 mg/kg) at 30 days and 40 days of age, and then again when they reached adulthood at 60 days of age. Adult rats received the same treatment at 60, 70 or 90 days of age. Based on earlier work in the laboratory, it was hypothesized that adolescent rats would show a greater pleasurable response to KET (greater 50 kHz USVs) and reduced aversion (reduced 22 kHz USVs). KET induced an increase in rewarding 50 kHz USVs that was similar in adolescents and adults. In contrast, as hypothesized, adults showed a greater number of aversive 22 kHz USVs in response to KET. These results demonstrate differences between adolescents and adults in the affective response to KET. Overall, KET appears to be more appealing to younger individuals than adults (equally rewarding but less aversive), which may help to explain the use of the drug by teens at dance clubs and raves.

Disclosures: R.M. Altamirano: None. **T.T. Towner:** None. **A. Escobedo:** None. **K.A. Trujillo:** None.

Poster

783. Adolescence and Addiction

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIDA Grant 3R01 DA030354

NIDA Grant 1R03 DA027457

Title: The potential influence of 5-httlpr genotype, gender and ecstasy use on depressive symptoms in adolescent and emerging adults

Authors: *N. E. WRIGHT, K. M. LISDAHL;
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Abstract: Objective: Lifetime ecstasy use among 12th graders is 5.6% (Johnston et al., 2015). Both ecstasy use and serotonin transporter gene (5-HTTLPR) have been associated with increased depressive symptoms (Starr et al., 2014; Matthews & Bruno, 2010). As ecstasy users frequently engage in polysubstance use (Martins, Mazzotti, & Chilcoat, 2005), a marijuana using control group is necessitated. Because gender may moderate interactions between ecstasy and 5-HTTLPR genotype (Price et al., 2013; Pardo-Lozano et al., 2012), this study examines independent and interactive effects of ecstasy use, 5-HTTLPR genotype and gender on depressive symptoms. Method: Forty-five controls (24 female, 21 male), 27 ecstasy users (9 female, 18 male), and 38 marijuana using-controls (13 female, 25 male) were balanced for 5-HTTLPR genotype (27 S carrier controls, 16 S carrier ecstasy users, 26 S carrier marijuana users). Exclusion criteria included co-morbid psychiatric and neurologic disorders (including major depressive disorder), prenatal problems, and excessive other-drug use. Multiple regressions were run to predict depressive symptoms from past year ecstasy, 5-HTTLPR status, gender, and ecstasy*5-HTTLPR and ecstasy*gender interactions, controlling for demographics and comorbid nicotine, alcohol and marijuana use. Results: Past year ecstasy use marginally predicted BDI symptoms ($p=.06$). Gender significantly predicted BDI symptoms ($p=.008$), with females experiencing more depressive symptoms. Past year ecstasy use interacted with gender to predict BDI scores ($p=.01$), with female ecstasy users demonstrating more depressive symptoms than female non-users. 5-HTTLPR genotype did not independently or interactively predict BDI symptoms ($p>.05$). Conclusions: Results demonstrated gender and ecstasy use independently and interactively predicted increased depressive symptoms in adolescents and young adults. Despite previous findings, 5-HTTLPR genotype was not associated with depressive symptoms in this sample. Therefore prevention efforts regarding ecstasy use should be aimed at young adults, particularly females, to reduce potential mental health burden. Implications and future directions will be further discussed.

Disclosures: **N.E. Wright:** None. **K.M. Lisdahl:** None.

Poster

783. Adolescence and Addiction

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Topic: C.17. Drugs of Abuse and Addiction

Support: Plan Nacional Sobre Drogas 2012I102

Plan Nacional de Investigación Científica (SAF2013-46135-P)

SGR1081

Title: Alcohol enhances mephedrone-induced signs of neurotoxicity and impaired neurogenesis in adolescent CD-1 mice

Authors: *A. M. CIUDAD, L. DUART, J. CAMARASA, E. ESCUBEDO, D. PUBILL; Univ. of Barcelona, Barcelona, Spain

Abstract: Neurotoxicity of amphetamine derivatives is a matter of concern and has been subject of a great amount of studies. Recently, a new family of amphetamine derivatives under the name of cathinones, mephedrone (Meph) being the most widely consumed, broke into the illegal market. In light of the fact that around 95% of cathinone consumers have been reported to combine them with alcohol (EtOH), we sought to study the consequences of the concomitant consumption of ethanol on mephedrone-induced neurotoxicity. Adolescent (5 weeks) male Swiss-CD1 mice were treated q.i.d. with a dose of Meph 25 mg/kg and 4 doses of EtOH (2; 1.5; 1.5; 1 g/kg; obtaining a steady plasma concentration of around 1.5 g/l) each separated by 2 hours in a room with set temperature at 27ºC, emulating typical ambient conditions found in dance clubs. Several neurochemical, histological and behavioral parameters were measured. The concomitant administration of EtOH enhanced Meph-induced decreases in tryptophan hydroxylase and SERT density in the hippocampus by 2-fold 7 days post-treatment (PT). Furthermore, these decreases correlated with a 2-fold increase in lipid peroxidation, measured as concentration of malondialdehyde (MDA) 24 hours PT. In a separate treatment, animals were injected with Bromo-deoxy-Uridine (BrdU) and sacrificed 28 days PT, with the objective of measuring neurogenesis in the dentate gyrus. During this time period, animals underwent a general Morris water maze (MWM) protocol, starting on day 7 PT. MWM showed an effect of Meph treatment on multiple learning and memory parameters, which matched with a BrdU count 25% lower than that of control animals. These changes were enhanced in the Meph+EtOH group, which showed a decerease higher than 2-fold in BrdU labelling. The decrease in hippocampal neurogenesis 28 days PT in Meph-treated animals and its potentiation by EtOH could be caused by a decrease in cell proliferation, increase in cell death, or a combination of both factors. This effect was accompanied by similar decreases in serotoninergic markers, pointing to a clear enhancement of Meph-induced neurotoxicity by EtOH, which could be directly related with the increase shown in oxidative stress. These results are of special significance, since alcohol is widely co-abused with amphetamine derivatives such as mephedrone, especially during adolescence, a crucial stage in brain maturation. This is especially noteworthy, since the

hippocampus is greatly involved in learning and memory processes, and could affect normal brain development in young adults, as suggested by results obtained in the MWM paradigm.

Disclosures: **A.M. Ciudad:** None. **L. Duart:** None. **J. Camarasa:** None. **E. Escubedo:** None. **D. Pubill:** None.

Poster

784. Monoamines and Behavior: Serotonin and Histamine

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 784.01/K18

Topic: C.18. Behavioral Pharmacology

Title: A study of the selective 5-HT2c agonists lorcaserin and CP809101 on side-effect profile, CNS penetration and functional selectivity

Authors: *G. A. HIGGINS[1,2], L. B. SILENIEKS[3], A. PATRICK[3], I. A. M. DELANNOY[3], P. J. FLETCHER[4], L. A. PARKER[5], N. J. MACLUSKY[5], L. C. SULLIVAN[6], T. A. CHAVERA[6], K. A. BERG[6];
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Abstract: Clinical experience with the 5-HT2C receptor agonist lorcaserin (LOR) has identified efficacy in the treatment of obesity and smoking cessation, with a primary dose-limiting side-effect of nausea and headache. We previously reported that the highly selective 5-HT2C agonist CP809101 (CP) may induce fewer signs of malaise/nausea in rats, suggesting potential for 5-HT2C agonists with improved side-effect profiles. We have adopted three lines of enquiry to further investigate. Firstly, we examined LOR and CP in the conditioned taste reactivity model, a validated rodent test to study nausea. Secondly, we compared plasma:CSF levels of LOR and CP at doses and timepoints relevant to the in-vivo studies. Male, Sprague-Dawley rats were used for all in-vivo studies. Thirdly, we compared the signaling profiles of LOR and CP at h5-HT2C receptors to look at evidence for functional selectivity differences between these two compounds. In the taste reactivity model, LOR (1-6 mg/kg SC) produced a dose-related incidence of conditioned gaping, equivalent to lithium chloride. This effect of LOR was reversed by SB242084 (0.5 mg/kg) confirming 5-HT2C receptor involvement. CP (3-12 mg/kg SC) produced a significantly smaller incidence of gapes (Veh: 0.3+0.3; LOR 6 mg/kg: 13.1+0.3; CP 12 mg/kg: 3.9+1.5; $P<0.05$). In CHO cells stably expressing h5-HT2C receptors, both LOR and CP produced a dose related increase in IP accumulation and arachidonic acid release, consistent

with PLC and PLA2 activation respectively. ERK levels were also increased by both drugs. In each case the EC50 for CP was 5-10x greater (i.e. more potent) compared to LOR, with similar efficacy relative to 5-HT. Finally, plasma and CSF levels of LOR and CP were measured. LOR (0.3-6 mg/kg SC) produced a dose-related increase in plasma and csf concentration with a peak at 1h, and plasma:CSF ratio of 0.1-0.2. In contrast, CP had a more shallow dose-response although plasma:CSF ratio was similar to LOR. These results suggest that differences between LOR and CP on measures of nausea may be unrelated to signaling profiles at the 5-HT2C receptor, but may be reflective of CSF levels and consequent 5-HT2C receptor occupancy and activation.

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Poster

784. Monoamines and Behavior: Serotonin and Histamine

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 784.02/K19

Topic: C.18. Behavioral Pharmacology

Support: NIH Grant DA030618

Title: Serotonin receptor 2C agonists lorcaserin and CP-809101 block cue-induced reinstatement of sugar-seeking behavior in rats

Authors: *E. ALTHERR[1], L. B. SILENIEKS[2], G. A. HIGGINS[2,3], P. J. FLETCHER[5,4], W. E. PRATT[1];
[1]Wake Forest University/Dept. Psychology, Winston-Salem, NC; [2]InterVivo Solutions Inc, Toronto, ON, Canada; [3]Pharmacol., [4]Departments of Pharmacol. and Toxicology, Univ. of Toronto, Toronto, ON, Canada; [5]Biopsychology, CAMH, Toronto, ON, Canada

Abstract: A main challenge for those intending to lose weight by dieting is to resist the temptation of preferred, highly caloric foods despite continued exposure to food and with cues associated with food. Manipulations of serotonin (5-hydroxytryptamine, 5-HT) signaling have been shown to affect a variety of motivated behaviors. In particular, the 5-HT2C receptor has been implicated as a therapeutic target for weight loss, and lorcaserin (Lorquess; Belviq) has been approved for the treatment of obesity. However, although the anorectic effects of 5-HT2C receptor stimulation have been well-described, recent research has also shown that 5-HT2C

agonists reduce reinstatement of nicotine-seeking in the presence of drug cues, which suggests that lorcaserin may also aid in weight loss due to inhibition of food-seeking in the presence of food-associated cues. In these experiments, we examined the impact of lorcaserin and the highly selective 5-HT2C agonist CP-809101 on 1) cue-induced reinstatement of sugar-seeking behavior, and 2) 2-hr food intake in rats on a 22-h deprivation schedule. Male Sprague-Dawley rats (N = 12/group) were food-deprived and trained to lever press for sugar pellets in the presence of a light/tone cue (for details, see Lin & Pratt, 2013). Once trained, rats underwent daily 20-min extinction sessions in which lever presses resulted in no programmed consequences. Upon extinguishing to 10% of their pre-extinction performance, rats received two separate reinstatement sessions following drug or saline injections (counterbalanced across rats and separated by 48 hr) in which lever pressing resulted in delivery of the light/tone cue. Prior to these reinstatement tests, rats received SC injections of saline or drug (Groups 1-3: lorcaserin at 0.1, 0.3, & 0.6 mg/kg; Group 4; CP-809101 at 1 mg/kg). Lorcaserin at 0.3 and 0.6 mg/kg (but not 0.1 mg/kg) significantly blocked cue-induced reinstatement of lever pressing to the sugar-associated cues, as did the 1 mg/kg of CP-809101 (e.g., reinstatement under vehicle: 88.4± 13.4 lever presses; Lor 0.6 mg/kg: 43.2±6.5 lever presses; CP 1 mg/kg: 48.0±9.5 lever presses). Notably, these effects occurred at doses of the 5-HT2C receptor agonists that were subthreshold to the anorectic effects of the drugs, as none of the doses tested in the reinstatement paradigm affected 2-hr food intake in animals tested under a 22-hr food deprivation schedule (e.g. Veh: 21.3±0.9g, Lor 1 mg/kg: 21.2±1.3g; NS). These data suggest that the therapeutic efficacy of 5-HT2C receptor agonists may include inhibition of the appetitive aspects of food-directed motivation.

Disclosures: E. Altherr: None. **L.B. Silenieks:** None. **G.A. Higgins:** None. **P.J. Fletcher:** None. **W.E. Pratt:** None.

Poster

784. Monoamines and Behavior: Serotonin and Histamine

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Program#/Poster#: 784.03/K20

Topic: C.18. Behavioral Pharmacology

Support: NSERC

CIHR

Title: The role of the 5-HT2C receptor in mediating the effects of acutely increased serotonin on incentive motivation

Authors: *C. BROWNE[1], P. J. FLETCHER[2,3,4];
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Abstract: Elevations in whole-brain serotonin (5-hydroxytryptamine; 5-HT) through systemic treatment with drugs such as d-fenfluramine or SSRIs generally inhibit reward-related behaviours. Similarly, selective activation of the 5-HT2C receptor suppresses feeding behaviour and responding for primary rewards such as food or drugs of abuse. This suggests a candidate mechanism by which 5-HT influences motivational processes through 5-HT¬2C receptors. We examined whether the 5-HT2C receptor broadly mediated the effects of 5-HT on incentive motivation based on responding for three different types of reinforcers: a primary reinforcer (saccharin), a conditioned reinforcer (CR), and a sensory reinforcer (SR). Saccharin has high intrinsic value and elicits proportionally high responding, a CR has learned value through a Pavlovian association with saccharin, and a SR presumably has some intrinsic salience allowing it to support responding. We first examined the effect of increased extracellular 5-HT with the SSRI citalopram (CIT) on responding for these reinforcers, and subsequently examined whether the selective 5-HT2C receptor antagonist SB242084 could block this effect. Lever pressing for saccharin, a CR, and a SR was examined in three separate cohorts of 12 male C57BL/6 mice, all of which were water restricted throughout testing. Responding for saccharin (0.1 ml, 0.2%) was first acquired on a fixed-ratio 1 (FR1) schedule of reinforcement and then tested on a random ratio 4 (RR4) schedule. For responding for a CR, mice first underwent 14 Pavlovian conditioning sessions wherein saccharin availability was signaled by a conditioned stimulus, forming a stimulus-reward association. Subsequently, responding for the conditioned stimulus alone (now a CR) was examined on a RR2 schedule. Responding for a SR was first acquired on an FR1 schedule and tested on a RR2 schedule. Following baseline testing for each reinforcer, the effects of CIT (10, 20 mg/kg; i.p.) on responding was first examined. Next, the ability of SB242084 (1 mg/kg) to block the effect of 10 mg/kg CIT was examined. Both 10 and 20 mg/kg CIT significantly reduced responding for all three types of reinforcers. Pre-treatment with SB242084 completely blocked the effect of CIT on responding for a CR and a SR, but did not block the effect of CIT on responding for saccharin. These results show that 5-HT regulates incentive motivation through activity at the 5-HT2C receptor. However, the ability of SB242084 to block the effects of elevated 5-HT in a reinforcer-specific manner suggests that the 5-HT2C receptor may mediate incentive motivational processes based on the type of reinforcer examined or its incentive value.

Disclosures: C. Browne: None. **P.J. Fletcher:** None.

Poster

784. Monoamines and Behavior: Serotonin and Histamine

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 784.04/K21

Topic: F.03. Motivation and Emotion

Title: Serotonin 2c receptor constitutive activity and behavior: the effect of an agonist, antagonist and inverse agonist on locomotor activity and responding for a conditioned reinforcer in mice

Authors: *C. HARVEY-LEWIS[1], C. J. BROWNE[2], G. A. HIGGINS[5,3], P. J. FLETCHER[1,2,4]; [1]Biopyschology, Ctr. for Addiction and Mental Hlth., Toronto, ON, Canada; [2]Dept. of Psychology, [3]Dept. of Pharmacol. and Toxicology, [4]Dept. of Psychiatry, Univ. of Toronto, Toronto, ON, Canada; [5]Intervivo Solutions, Toronto, ON, Canada

Abstract: A large literature exists on the effects of pharmacological activation of the serotonin 2c (5-HT2c) receptor on reward-related processes. However, less is known about the influence of constitutive activity of the 5-HT2c receptor on behavior. The 5-HT2c receptor can spontaneously activate intracellular signaling pathways (constitutive activity) *in vitro*; this may facilitate mesolimbic dopaminergic release *in vivo* (Deurwaerdère et al. 2004). However, no direct behavioral output of 5-HT2c receptor constitutive activity has been reported. Here, we investigate the effect of 5-HT2c receptor constitutive activity on two dopaminergic-dependent behaviors - responding for a conditioned reinforcer (CR) and locomotor activity - using a highly selective 5-HT2c agonist (CP809101), the putative 'silent' antagonist (SB242084) and putative inverse agonist (SB206553). Mice received 14days of non-contingent Pavlovian association between a CS (5s cue light and sound of dipper) and delivery of 0.1ml 0.2% saccharin. Mice were then trained on a two-lever task where active lever responses resulted in presentation of the CS (now a CR) without saccharin delivery and inactive lever responses had no consequences. Animals were treated with CP809101 (0-3mg/kg), SB242084 (0-1mg/kg) or SB206553 (0-10mg/kg) prior to testing. A second cohort was habituated to the locomotor testing apparatus for 5 days. These animals received the same dosing procedure as the first cohort. CP809101 dose-dependently decreased CR-directed responding and locomotor activity. SB242084 dose-dependently increased both measures. SB206553 had no significant effects on locomotor activity but significantly decreased CR-directed responding at the 10mg/kg. In the second phase we attempted to block these effects to test 5-HT2c specificity. Pretreatment with silent doses of SB242084 blocked the CP809101-induced decreases in locomotor activity and responding for a CR. However, SB242084 pretreatment had no effect on SB206553 induced decreases in CR-directed responding. Additionally, SB206553 pretreatment did not block CP809101- or SB242084-induced behavioral effects. The opposing behavioral effects of SB242084 and CP809101 highlight the importance of 5-HT2c receptors in motivational processes. Furthermore, the observed effects of SB242084 on locomotion and CR-directed responding provide support that endogenous tone at the 5-HT2c receptor can directly influence dopaminergic-dependent

behaviors. Unlike previous *in vivo* and *in vitro* studies, mainly in rats, we failed to find evidence for inverse agonism of 5-HT2c receptors by SB206553 suggesting a possible strain difference in its effects.

Disclosures: C. Harvey-Lewis: None. **C.J. Browne:** None. **G.A. Higgins:** None. **P.J. Fletcher:** None.

Poster

784. Monoamines and Behavior: Serotonin and Histamine

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 784.05/K22

Topic: C.18. Behavioral Pharmacology

Title: Cognitive effects of AG-1 in the chronic low-dose (CLD) 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated macaque model of Parkinson's disease

Authors: *E. Y. PIOLI[1], S. CAMUS[1], J. YANG[1], Q. LI[1], A. CROSSMAN[1], E. BEZARD[1], S. HOGG[2];
[1]MOTAC, Manchester, United Kingdom; [2]Angita Pharmaceuticals B.V., Groningen, Netherlands

Abstract: Introduction. Parkinson's disease (PD), in which there is widespread degeneration of the catecholamine system, is characterized by both motor symptoms and impairment of both cognitive performance and executive functions. A strategy to improve both types of symptoms might be to combine dopamine D2 receptor agonism, to alleviate motor symptoms, with histamine H3 receptor antagonism, to improve cognition. The purpose of the study was to examine the cognitive effects of such a dual activity compound in the gold standard primate model of cognitive defects in PD, the so-called chronic low-dose (CLD) 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) macaque model. Methods. Cognitive performances were assessed in 3 behavioural tasks following administrations of AG-1 (0.03, 0.1 or 0.3 mg/kg). Four CLD cynomolgus macaques, displaying cognitive deficits and mild parkinsonian motor deficits, produced by chronic exposure to low doses of MPTP were tested in the Variable Delayed Response (VDR) and the Continuous Performance Task (CPT) on a touch-screen computerized system. Eight MPTP cynomolgus macaques, displaying more severe motor deficits, were tested in the Object Retrieval (OR) task. Results. In the OR task, AG-1 at 0.1 mg/kg significantly improved 1st attempt successes and correct responses by decreasing omissions compared to an optimal dose of L-DOPA. No significant overall effect of AG-1 was found on the VDR tasks. However, when performing a best dose analysis, AG-1 significantly improved the percentages of correct responses and decreased errors compared to vehicle in the VDR. In the CPT, AG-1 did

not show any positive effects. Conclusion. AG-1 improved cognitive performance of MPTP-treated monkeys in the OR and VDR tasks but not in the CPT. These results suggest the likely beneficial cognitive effects of AG-1 for patients with PD-mild cognitive impairments.

Disclosures: **E.Y. Pioli:** A. Employment/Salary (full or part-time):; Motac. **S. Camus:** A. Employment/Salary (full or part-time):; Motac. **J. Yang:** A. Employment/Salary (full or part-time):; Motac. **Q. Li:** A. Employment/Salary (full or part-time):; Motac. **A. Crossman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Motac. **E. Bezard:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Motac. **S. Hogg:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Angita Pharmaceuticals B.V.. F. Consulting Fees (e.g., advisory boards); Angita Pharmaceuticals B.V..

Poster

784. Monoamines and Behavior: Serotonin and Histamine

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 784.06/K23

Topic: C.18. Behavioral Pharmacology

Support: MH097012

R01DA035316

GM007767

GM039561

Title: Intrahippocampal injection of a small molecule RGS4/19 inhibitor has antidepressant-like effects in a mouse model

Authors: ***N. SENESE**[1], R. NEUBIG[2], J. TRAYNOR[1];
[1]Pharmacol., Univ. of Michigan, Ann Arbor, MI; [2]Michigan State Univ., East Lansing, MI

Abstract: Regulators of G-protein signaling (RGS) proteins are a large family of intracellular proteins that negatively regulate G-protein coupled receptor (GPCR) signaling to heterotrimeric G proteins. RGS proteins act as GTPase accelerating proteins (GAPs) and interact directly with active GTP-bound Gα subunits. This action enhances the hydrolysis of GTP to GDP, thus inactivating the Gα subunits and allowing reformation of the inactive Gα/β/γ-protein

heterotrimer. This allows RGS proteins to reduce both the duration and extent of GPCR signaling. We have demonstrated that mice expressing an RGS insensitive variant of Gαi2 (RGSi Gαi2; knock-in variant of Gαi2 with a single point mutation in the switch region that prevents interaction with all RGS proteins) exhibit an antidepressant-like phenotype in several behavioral tests. This phenotype is caused by increased signaling downstream of 5-HT1A receptors (5-HT1AR). In addition, we have shown in cultured hippocampal neurons that RGS19 is an effective inhibitor of 5HT1A receptor signaling. Furthermore evidence suggests that RGS4 and RGS6 are important modulators of antidepressant drug action. The present study sought to answer two questions: A) What is the location of the 5HT1ARs involved in the antidepressant-like phenotype in the RGSi Gαi2 mice and B) What information can be gained about the specific RGS proteins that are responsible for negative regulation of these 5HT1ARs. RGSi Gαi2 mutant mice show the expected antidepressant-like phenotype (reduced immobility) in the tail suspension test (TST) which is reversed by infusion of the selective 5-HT1AR antagonist WAY-100635 directly into the hippocampus. Conversely, direct hippocampal infusion of the 5-HT1AR agonist 8-OH-DPAT decreases immobility in wild type mice, and this is reversed by peripheral administration of WAY-100635. CCG-203769 is a small molecule RGS4 inhibitor with selectivity for RGS4 > RGS19 >> other RGS proteins. Intrahippocampal infusion of CCG-203769 over 3 days in wild-type mice produces a marked antidepressant-like activity in the TST. These findings identify hippocampal 5-HT1ARs specifically coupled to Gαi2 as important for the antidepressant-like effect in this phenotype and suggest RGS4 and/or RGS19 as RGS proteins that may regulate signaling through this pathway. These results identify proteins along this signaling pathway (5-HT1AR/Gαi2 complex, RGS4, RGS19) as potential targets for antidepressant medications.

Disclosures: **N. Senese:** None. **R. Neubig:** None. **J. Traynor:** None.

Poster

784. Monoamines and Behavior: Serotonin and Histamine

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 784.07/K24

Topic: C.18. Behavioral Pharmacology

Support: NIH Grant 5R01DA002925

Title: Behavioral effects of N,N-dialkyltryptamine hallucinogens in mice

Authors: ***L. M. KLEIN**[1], M. A. GEYER[2], A. L. HALBERSTADT[2];
[2]Psychiatry, [1]UC San Diego, San Diego, CA

Abstract: N,N-dialkyltryptamines are known to act non-selectively as agonists at 5-HT1A and 5-HT2A receptors. However, the contributions of these receptors to the behavioral effects of N,N-dialkyltryptamines are unclear. Recently, illicit sources have made available an expanded repertoire of N,N-dialkyltryptamines, including N,N-dimethyltryptamine (DMT) and homologues with one or both methyl groups extended to ethyl or propyl groups. In light of increasing use of these compounds, we investigated their behavioral pharmacology in mice. The head twitch response (HTR), a behavior mediated by 5-HT2A, is often used as a rodent proxy for hallucinogenic effects in humans. Using a head-mounted magnet and a magnetometer coil to detect head movement, we found that IP treatment with DMT (0.625-10 mg/kg), N-methyl-N-ethyltryptamine (MET; 0.625-10 mg/kg), N,N-diethyltryptamine (DET; 0.3-3 mg/kg), and N,N-dipropyltryptamine (DPT; 0.625-10 mg/kg) induced the HTR in C57Bl/6J mice, suggesting that activity at 5-HT2A contributes to the behavioral effects of these compounds. Additionally, the Behavioral Pattern Monitor (BPM) was used to assess the effects of DMT, MET, DET, and DPT on exploratory behavior. When administered at 30 mg/kg IP, all four compounds reduced locomotor activity and investigatory behavior. Since previous BPM experiments demonstrated tryptamine hallucinogens to reduce locomotor activity by activating 5-HT1A (Halberstadt et al., 2011), we assessed the contribution of 5-HT1A to these locomotor effects by comparing the effects of DMT, MET, DET, and DPT in 5-HT1A wild-type (WT) and knockout (KO) mice. Interestingly, the involvement of 5-HT1A in locomotor hypoactivity depended on the length of the N-alkyl groups. The effects of DPT were completely absent in 5-HT1A KO mice, while the effects of DET were partially attenuated in the KOs. By contrast, DMT and MET produced similar responses in WT and KO mice, and the effect of DMT was not blocked by the 5-HT1A antagonist WAY-100,635. Our findings demonstrate that the behavioral effects of N,N-dialkyltryptamines depend, at least in part, on the 5-HT2A receptor, and indicate a variable role for the 5-HT1A receptor depending on the length of the N-alkyl groups. Human clinical trials indicate subtle differences in the effects of DMT, DET, and DPT. In light of our findings, these subjective differences may result from differential interaction of these compounds with 5-HT1A. Experiments are in progress to determine the receptor(s) responsible for the effects of DMT and MET in the BPM.

Disclosures: L.M. Klein: None. **M.A. Geyer:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIDA, NIMH, U.S. Veteran's Administration VISN 22 Mental Illness Research, Education, and Clinical Center. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); San Diego Instruments. F. Consulting Fees (e.g., advisory boards); Abbott, Dart, Lundbeck, Neurocrine, Omeros, Otsuka, Sunovion. **A.L. Halberstadt:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds

come to an institution.; NIH, Brain & Behavior Research Foundation, Roche, L-3 Communications.

Poster

784. Monoamines and Behavior: Serotonin and Histamine

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 784.08/K25

Topic: C.18. Behavioral Pharmacology

Support: Capes

CNPq

Alexander von Humboldt Foundation

Title: Sex-dependent and specie-specific effects of fluoxetine on repeated forced swimming test in rodents: translational implications

Authors: *C. LINO DE OLIVEIRA[1,2,3], I. SPEZIA[1], L. C. THEINDL[1], F. B. L. CHRISTIAN[3], J. A. CADORE[3], P. R. SUMAN[2], K. DOMINGUES[2];
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Abstract: Repeated forced swimming test (rFST) is a modified version of the Porsolt test created to provide information about gradual effects of antidepressants. rFST is based in the paradigm that the repetition of forced swimming stress may increase immobility time facilitating the detection of antidepressants in rodents. Indeed, the immobility of rats (Wistar, adult, male) in rFST decreased when they were treated once a day for 1, 7 and 14 days with fluoxetine (FLX) or imipramine in doses that were, at least, ten times lower (2.5 and 5 mg/kg) than the daily doses effective in the Porsolt test [1,2,3]. Here, we investigated if the paradigm for the rFST could be translated from male to female rats of the same strain as well as to males of other species of laboratory rodents. Female Wistar rats (adults with or without ovarian failure, n=8/group) and Swiss mice (adults, males, n=8/group) were tested in rFST during the treatment (daily, p.o. for 7 or 14 days) with FLX (1-10 mg/kg) or sucrose 10%. Male Wistar rats treated with FLX (2.5 mg/kg) or sucrose 10% comprised the “positive” control group. The rFST for rats consisted of 15 min- swimming test (pretest) followed by a 5 min-swimming test in the first (test), seventh (retest 1) and fourteenth (retest 2) day after pretest. The rFST protocol for mice was similar to that for rats except that pretest was absent. Test sessions were videotaped for posterior extraction

of duration of immobility using the software Ethowatcher. For male and female rats, different of male mice, the treatment with sucrose seemed to neutralize the influence of the repetition of the forced swimming stress on immobility revealing a possible "placebo" effect of sucrose. The immobility time of females (with or without ovarian failure) remained unchanged in the rFST during the treatment with FLX (2.5 mg/kg) whereas in males it dropped in the retest 2, as expected [2,3]. However, the immobility time of female Wistar rats and male Swiss mice increased with the chronic treatment with FLX (10 mg/kg), as compared to acute-treated group, suggesting a paradoxical effect of FLX in these animals. These data suggest that rFST paradigm may be not directly translated from male rats to female rats or to male mice. In addition, rFST may detect sexual and specie-specific styles of coping with stress and response to antidepressants. Moreover, rFST in female Wistar rats or in male Swiss mice may provide strategies to discover new antidepressants. [1] Gutiérrez-García and Contreras 2009, Pharmacol Biochem Behav v91: 542-8; [2] Mezadri et al., 2011, J Neurosci Meth 195: 200-205; [3] Possamai et al. 2015, Prog Neuropsychopharmacol Biol Psychiatry. 2015 Apr 3;58:15-21. Financial Support: Capes, CNPq, AvH.

Disclosures: C. Lino De Oliveira: None. **I. Spezia:** None. **L.C. Theindl:** None. **F.B.L. Christian:** None. **J.A. Cadore:** None. **P.R. Suman:** None. **K. Domingues:** None.

Poster

784. Monoamines and Behavior: Serotonin and Histamine

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 784.09/K26

Topic: C.18. Behavioral Pharmacology

Title: AntiParkinsonian effects of AG-1 in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated macaque model of Parkinson's disease

Authors: *A. R. CROSSMAN[1], E. Y. PIOLI[2], D. W. KO[2], Q. LI[2], E. BEZARD[2], S. HOGG[3]; [1]The Univ. of Manchester, Manchester, United Kingdom; [2]MOTAC, Manchester, United Kingdom; [3]Angita Pharmaceuticals B.V., Groningen, Netherlands

Abstract: Introduction. Parkinson's disease (PD), in which there is widespread degeneration of the catecholamine system, is characterized by motor symptoms and impairment of both cognitive performance and executive functions. A strategy to improve both types of symptoms might be to combine dopamine D2 receptor agonism, to alleviate motor symptoms, with histamine H3 receptor antagonism, to improve cognition. The purpose of the study was to examine the antiparkinsonian effects of such a compound in the gold standard primate model of PD, the so-

called MPTP macaque model. Methods. Parkinsonian symptoms were produced in 6 cynomolgus macaques by daily administration of MPTP (0.2 mg/kg, i.v.). Regular treatment with L-DOPA resulted in the development of dyskinesia. PD motor disability, dyskinesia and on-time were assessed following administration of AG-1 (0.03, 0.1, 0.3 mg/kg) in comparison to L-DOPA and pramipexole. Results. AG-1 showed a full anti-parkinsonian effect at 0.3 mg/kg with reduction of the disability, bradykinesia, posture scores and a long lasting effect of at least 10 hours. However, it induced also some dyskinesia as animals were primed. The 0.1 mg/kg dose produced a similar anti parkinsonian effect to L-DOPA. Conclusion. These results suggest the likely beneficial effects of AG-1 on motor symptoms of PD patients.

Disclosures: **A.R. Crossman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Motac. **E.Y. Pioli:** A. Employment/Salary (full or part-time):; Motac. **D.W. Ko:** A. Employment/Salary (full or part-time):; Motac. **Q. Li:** A. Employment/Salary (full or part-time):; Motac. **E. Bezard:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Motac. **S. Hogg:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Angita Pharmaceuticals B.V.. F. Consulting Fees (e.g., advisory boards); Angita Pharmaceuticals B.V..

Poster

784. Monoamines and Behavior: Serotonin and Histamine

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 784.10/K27

Topic: C.18. Behavioral Pharmacology

Support: The Swedish Research Council (K2013-61X-14961-07-3)

Söderberg's Foundation (MT-30/09)

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Title: Serotonin depletion eliminates sex differences with respect to contextual fear in rat

Authors: *R. PETTERSSON, M. HAGSÄTER, E. ERIKSSON;
Pharmacol., Gothenburg, Sweden

Abstract: Supporting the hypothesis that serotonin is important for upholding sex differences in behavior, we recently showed that serotonin depletion, obtained by means of the serotonin synthesis inhibitor para-chlorophenylalanine (PCPA), eliminates sex differences in anxiety-like behavior as assessed using the elevated plus maze in rat. In the present study, we compared male and female rats with respect to two other anxiety-related aspects of behavior, i.e. immobility and startle responses to sudden noise bursts, and to what extent any possible sex difference in this regard could be influenced by serotonin depletion. The two sexes differed markedly with respect to immobility after contextual conditioning induced by previous exposure to foot shocks in the sense that males displayed more immobility than females. This response was reduced by PCPA in males but not females, the result being that serotonin-depleted animals displayed no sex difference. PCPA was found to enhance startle responses in context-conditioned males and in non-conditioned females, respectively. After context conditioning males given saline, but neither females, nor PCPA-treated males, showed a negative correlation between startle and immobility, suggesting the latter behavior, when excessive, to interfere with the former. We suggest that a clear-cut sex difference in a putatively anxiety-related behavior, i.e. context-conditioned immobility, is to a large extent caused by an "anxiogenic" serotonergic influence being stronger in males than in females. The results are well in line with the theory that an important role of serotonin is to uphold certain sex differences in behavior.

Disclosures: **R. Pettersson:** None. **M. Hagsäter:** None. **E. Eriksson:** None.

Poster

785. Monoamines and Behavior: Dopamine and Norepinephrine

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 785.01/K28

Topic: C.18. Behavioral Pharmacology

Support: NIAAA/NIH AA022448

NIAAA/NIH AA017243

Title: Role of purinergic p2x4 receptors in regulating signaling cascades and behaviors dependent upon dopamine receptor activity

Authors: *S. KHOJA[1], L. ASATRYAN[2], M. W. JAKOWEC[3], D. L. DAVIES[2];
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Abstract: Purinergic P2X4 receptors (P2X4Rs) are adenosine-5'-triphosphate (ATP) activated ion channels. They are expressed on multiple types of cells across the central nervous system (CNS) yet their roles in mediation of physiological responses are less explored. Previous reports link P2X4Rs to neuropathic pain, neuroendocrine effects and hippocampal synaptic plasticity. Findings from our group, using gene knockout strategy [i.e. P2X4R knockout (KO) mice] suggest that P2X4Rs play a role in sensorimotor gating, social behavior and ethanol drinking behavior. P2X4Rs may mediate these behaviors via interactions with glutamate and GABAergic systems though pre- and postsynaptic mechanisms and /or via modulation of dopamine (DA) neurotransmission. We recently found that P2X4R KO mice have altered expression of DA markers including tyrosine hydroxylase, dopamine transporter and dopamine D1, D2 receptors (D1Rs and D2Rs) in basal ganglia, implying imbalances in DA homeostasis. The current investigation tests the hypothesis that altered DA homeostasis affects signaling pathways in striatum and this underlies sensorimotor gating deficits in P2X4R KO mice. We measured phosphorylation of DA and cyclic AMP regulated phosphoprotein-32kDa (DARPP-32), cAMP response element binding protein (CREB) in striatum of P2X4R KO and WT mice using Western blotting. We also studied the responses of P2X4R KO mice to DA antagonists in prepulse inhibition (PPI) of acoustic startle, an operational measure of sensorimotor gating. In the dorsal striatum of P2X4R KO mice, DARPP-32 phosphorylation was significantly increased and the opposite effect was seen in ventral striatum. There was significant increase in CREB phosphorylation in both striatal regions of P2X4R KO mice. Sensorimotor gating deficits were rescued by D2R antagonist, raclopride but not by D1R antagonist, SCH 23390, implying DA dysregulation as a mechanism for behavioral deficit. The findings supports hypothesis that altered DA receptor expression in P2X4R KO mice dysregulates DA dependent signaling cascades and alters responses to DA antagonists. These results highlight an important role for P2X4Rs in maintaining DA homeostasis and illustrate how their deficiency induces behavioral manifestations characteristic of DA dysfunction.

Disclosures: **S. Khoja:** None. **L. Asatryan:** None. **M.W. Jakowec:** None. **D.L. Davies:** None.

Poster

785. Monoamines and Behavior: Dopamine and Norepinephrine

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 785.02/K29

Topic: C.18. Behavioral Pharmacology

Title: Attenuation of amphetamine-induced recovery from neglect with noradrenergic antagonists

Authors: *M. J. HYLIN[1], M. BRENNEMAN[2], J. CORWIN[3];
[1]Psychology, Southern Illinois Univ., Carbondale, IL; [2]Psychology, Coastal Carolina Univ., Conway, SC; [3]Psychology, Northern Illinois Univ., DeKalb, IL

Abstract: Neglect is a human neurological disorder typically produced by stroke that is characterized by an inability to attend or orient toward stimuli presented in the contralesional hemispace. Current treatments for neglect are limited in their effectiveness. Damage to the medial agranular cortex (AGm) in rodents produces severe multimodal neglect of visual, tactile, and auditory stimulation with deficits that are similar to those seen in humans. Amphetamine treatment has been shown to result in recovery from motor, visual, and spatial deficits. Recently, it has been observed that systemic injections of amphetamine produce long-lasting, relatively stable recovery from AGm-induced neglect. Prior research has indicated that treatments that affect norepinephrine produce recovery similar to that resulting from amphetamine administration, which has led to the hypothesis that amphetamine-induced recovery is due to noradrenergic mechanisms. However, no prior studies have directly tested this hypothesis. Because amphetamine results in stable and relatively permanent recovery from neglect, the purpose of the current study was to investigate whether noradrenergic receptor mechanisms are responsible for amphetamine-induced recovery from neglect. In order to block α- or β-adrenergic receptors, subjects were given an injection of a α-adrenergic antagonist (phenoxybenzamine), β-adrenergic antagonist (propranolol) or saline prior to each administration of amphetamine. Co-administration of either noradrenergic antagonist prior to amphetamine administration significantly delayed or blocked amphetamine-induced recovery. Amphetamine treatment alone induced recovery from neglect within two weeks. The results of the current study indicate that α- and β-adrenergic receptors are crucial factors in amphetamine-induced recovery from neglect in rats.

Disclosures: M.J. Hylin: None. **M. Brenneman:** None. **J. Corwin:** None.

Poster

785. Monoamines and Behavior: Dopamine and Norepinephrine

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 785.03/K30

Topic: C.18. Behavioral Pharmacology

Title: Preclinical telemetric electroencephalography (EEG) and *in vivo* microdialysis to study dopaminergic hyperactivity in freely moving rats

Authors: M. SHIMASAKI, C. HOYLE, P. VOEHRINGER, *B. FERGER;
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Abstract: Dopamine (DA) is a key regulator of cognition, mood, reward and movement in the human and rodent brain. The DA homeostasis is tightly controlled by the dopamine transporter (DAT), which is a target for addictive drugs including cocaine. The present study was designed to investigate the effects of cocaine in freely moving rats using telemetric electroencephalography (EEG) and *in vivo* microdialysis in the nucleus accumbens shell. Extracellular cocaine levels were measured by LC-MS-MS and dopamine levels by HPLC coupled to electrochemical detection. Behaviour was assessed by an automated motor activity system and light beam interruptions. Cocaine (5, 10 and 15 mg/kg, i.p.) dose dependently induced an increase in motor activity, which reached its maximum level after 20 min and lasted for 90 min. Almost in parallel, extracellular dopamine levels showed a peak concentration at 30 min and then returned to basal levels 120 min later. Maximum cocaine levels measured from the dialysates appeared 30 min after dosing (300 nmol/l). In addition, cocaine appeared to affect the EEG power spectrum, increasing gamma frequency band power (40-80 Hz) up to 60 min after administration, whilst causing a decrease of power in delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), and beta (13-40 Hz) frequencies. In conclusion, these results indicate that cocaine induces an increase in dopaminergic transmission in the nucleus accumbens shell, and as expected, produces hyperactivity. Similarly, the effect observed on the EEG frequency bands highlights a possible role in the cocaine-induced arousal behavior, which could serve as a physiological biomarker of target and pathway engagement studies in drug discovery.

Disclosures: M. Shimasaki: A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co KG. **C. Hoyle:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co KG. **P. Voehringer:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co KG. **B. Ferger:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co KG.

Poster

785. Monoamines and Behavior: Dopamine and Norepinephrine

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 785.04/K31

Topic: C.18. Behavioral Pharmacology

Title: High dose propranolol, a beta adrenergic blocker for the control of violence and self abuse in patients with autism spectrum disorders

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Abstract: Uncontrolled aggression (including self abuse) is a behavior which transcends diagnostic labels. This symptom is of utmost clinical importance and yet is rarely the end point of clinical trials. The antipsychotic medications, which are most frequently used, are sometimes successful however many subjects are not adequately treated and many experience unacceptable side effects to those medications. Propranolol a lipophilic beta adrenergic antagonist, has been shown in anecdotal reports dating back to the 1970's to be very successful in controlling intractable violence in various diagnoses. A retrospective chart review is presented of 46 subjects with Autism Spectrum Disorders who had violent behavior (aggression and or self abusive behaviors) which were refractory to treatments including behavioral treatment as well as at least one anti-psychotic medication. All of these behaviors were of high severity (CGI-S 5,6 or 7, markedly, severely or extremely ill) prior to the addition of the propranolol. 85% of the cases (39/46) were much or very much improved when adding propranolol to other medications which had shown some degree of success. Notably, 1) in many cases attempts to discontinue the other medications after the administration of propranolol failed; 2) only rarely did propranolol show benefit below 300 mg/day and often benefit was often not noted until reaching significantly higher doses; 3) other serious symptoms such as hyperactivity, compulsive and repetitive behaviors and mood related behaviors were often refractory to the propranolol. The mechanism of action of the high dose propranolol is not clear. Its sympatholytic properties may be responsible for this benefit; however the peripheral effects of propranolol occur at much lower doses. Central mechanisms need to be considered. One mechanism might be propranolol's blocking the reconsolidation of fearful memories as noted in PTSD. These "fearful" tracings might be consolidated routinely as subjects with ASD appear to be in a chronic hyperadrenergic state.

Disclosures: E.B. London: None.

Poster

785. Monoamines and Behavior: Dopamine and Norepinephrine

Location: Hall A

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Topic: C.18. Behavioral Pharmacology

Support: NIH T32 MH065215 Postdoctoral Training Program in Functional Neurogenomics

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Title: Not all it's cracked up to be: The human DAT coding variant Val559 eliminates cocaine-induced locomotor activation despite normal cocaine place preference conditioning

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Abstract: The presynaptic dopamine (DA) transporter (DAT, SLC6A3) plays a critical role in clearing synaptic DA and is a direct target of psychostimulant drugs. Previously, we identified a rare, nonsynonymous SLC6A3 variant (DAT Val559) in two male siblings diagnosed with attention-deficit hyperactivity disorder (ADHD) that was previously found in subjects with bipolar disorder (BPD), and more recently has been identified in subjects with autism spectrum disorder. *In vitro* characterization of the mutant transporter revealed normal protein expression and trafficking as well as intact DA uptake. However, DAT Val559 exhibits anomalous DA efflux (ADE) and lacks amphetamine (AMPH)-stimulated DA release. To more closely link DAT dysfunction to pathogenic mechanisms underlying neuropsychiatric illness, we generated a knock-in mouse model harboring the DAT Val559 mutation (Mergy et al., PNAS 2014). In the striatum of these mice, we found elevated basal levels of extracellular DA that rose less significantly in response to amphetamine (AMPH) as compared to elevations seen in WT animals. Similarly, horizontal and vertical locomotor hyperactivity resulting from acute challenge with submaximal doses of AMPH or methylphenidate (MPH) was blunted in the DAT Val559 mice. Here we report that, in contrast to our findings with AMPH and MPH, the locomotor-stimulating actions of cocaine, as well as the ability of the drug to promote rearing and stereotypic behaviors, are completely absent in DAT Val559 mice. Though the psychomotor response to cocaine is lost in these animals, the rewarding properties of the drug remain intact as evidenced by WT levels of conditioned place preference (CPP) for cocaine. Further, we found extinction of cocaine CPP to be delayed in mice homozygous for the mutant allele. Thus, the dysfunction in DA homeostasis that results from this single DAT point mutation differentially impacts two prominent dimensions of cocaine action. Ongoing efforts seek to determine the neuroanatomical, biochemical and physiological determinants of these differential perturbations in cocaine response. Though the basis of these divergent behavioral outcomes remains unclear, the DAT Val559 mouse model appears to provide an unexpected opportunity to dissect the distinct mechanisms underlying the complex actions of cocaine, studies that may reveal further dimensions of risk for neuropsychiatric disorders linked to DA signaling dysfunction.

Disclosures: **A. Stewart:** None. **G.L. Davis:** None. **R. Gowrishankar:** None. **P.J. Gresch:** None. **M.K. Hahn:** None. **R.D. Blakely:** None.

Poster

785. Monoamines and Behavior: Dopamine and Norepinephrine

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 785.06/K33

Topic: C.18. Behavioral Pharmacology

Support: NIH Grant DA020802

Title: Conditioning and sensitization of dopamine antagonist effects on open field activity

Authors: *H. S. WIRTSHAFTER[1,2], D. WIRTSHAFTER[2];
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Abstract: Hyperactivity induced by dopamine agonists can be conditioned to contextual cues, and conditioning may play a role in the locomotor sensitization seen after repeated administration of these drugs. However few studies have investigated if conditioning mechanisms play a similar role in the hypoactivity induced by dopamine antagonists. We report a series of studies investigating these topics. In the first experiment, two groups of rats received four daily 10 min open field activity tests. The experimental (EXP) group received haloperidol (HAL) (0.2 mg/kg, s.c.) 30 min before testing and saline 30 min later. The control (CON) group received the injections in the reversed order. Activity remained stable in the CON animals, but declined steadily across days in the EXP rats. On day 5, all rats received saline prior to testing. In the absence of drug treatment, latency to initiate movement was significantly increased and numbers of rears decreased in the EXP as compared to the CON rats. This finding demonstrates that aspects of HAL-induced hypoactivity can be conditioned to environmental or procedural cues. The second experiment was similar to the first, but subjects in both groups received an injection of HAL prior to test day 4. Although the same drug treatments were administered on the test day, latency to initiate movement was significantly longer, and activity and rearing counts lower, in the EXP than CON animals. These results demonstrate context dependent sensitization of HAL induced hypoactivity. In the third experiment, all rats received HAL injections prior to open field tests over four days of testing. Conditioned responses to HAL were then extinguished in the EXP subjects by testing them for 4 days in the open field following saline injections. The CON animals were injected and returned to their home cages. Activity increased steadily across the four extinction tests in the EXP animals, documenting extinction of the drug response. On the final (9^{th}) day all rats were injected with HAL prior to testing. Under

these conditions activity was higher in the EXP animals, demonstrating that contextual conditioning underlies much of the sensitization seen after repeated HAL injections. These studies demonstrate that HAL-induced hypoactivity increases with repeated testing. Conditioning of the drug response to contextual or procedural cues can mediate this effect. Clinically, analogous factors may play a role in the therapeutic lag observed with neuroleptics. The ability of dopamine antagonists to produce incremental extinction-like effects on operant behavior may also be the result of similar conditioning effects.

Disclosures: H.S. Wirtshafter: None. **D. Wirtshafter:** None.

Poster

785. Monoamines and Behavior: Dopamine and Norepinephrine

Location: Hall A

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Topic: C.18. Behavioral Pharmacology

Support: NSERC Discovery Grant

NSERC CGSD

Title: Pharmacological manipulation of the dopaminergic system: An investigation of alcohol's locomotor stimulant effect in zebrafish

Authors: *S. TRAN[1], M. NOWICKI[2], A. MURALEETHARAN[2], D. CHATTERJEE[2], R. GERLAI[1,2];
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Abstract: Alcohol is the world's most commonly consumed drug despite its potential abuse. In humans, individual variation in how people respond to alcohol's stimulant effect has been suggested to be a risk factor for the development of alcohol addiction, yet the exact mechanism by which alcohol increases locomotor activity remains unknown. Using zebrafish, we focus on the dopaminergic system as a potential mediator for alcohol induced locomotor activity. Previous studies with zebrafish have shown that similarly to mammals, alcohol increases the total distance traveled as well as whole-brain dopamine levels and tyrosine hydroxylase activity, the rate-limiting enzyme responsible for dopamine synthesis. These studies suggest a relationship between activation of the dopaminergic system and alcohol's locomotor stimulant effect in zebrafish. Using a pharmacological approach we examine whether dopamine D1 receptor

activation and tyrosine hydroxylase phosphorylation contributes to alcohol's stimulant effect. Zebrafish exposed to 1% v/v ethanol were shown to increase the total distance traveled as well as whole-brain dopamine levels compared to controls. Pre-treatment with the D1-R antagonist (SCH-23390) or with phosphorylated tyrosine hydroxylase inhibitor (tetrahydropapaveroline) attenuated the alcohol induced increase in locomotor activity. In addition, although both pre-treatments reduced whole-brain dopamine levels, the effect of the D1-R antagonist was independent of alcohol exposure. The results suggest that in zebrafish, alcohol's locomotor stimulant effect is partially mediated through both tyrosine hydroxylase phosphorylation and dopamine D1 receptor activation, but the role of dopamine itself remains unclear. Overall, we provide support for the notion that alcohol's locomotor stimulant effect is partially mediated via the dopaminergic neurotransmitter system.

Disclosures: S. Tran: None. **M. Nowicki:** None. **A. Muraleetharan:** None. **D. Chatterjee:** None. **R. Gerlai:** None.

Poster

785. Monoamines and Behavior: Dopamine and Norepinephrine

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Topic: C.18. Behavioral Pharmacology

Support: Intramural Research Grant for Neurological and Psychiatric Disorders of NCNP

Health and Labour Sciences Research Grants

the Strategic Research Program for Brain Sciences by the Ministry of Education, Culture, Sports, Science and Technology of Japan

Title: Possible role of the dopamine D1 receptor in the sensorimotor gating deficits induced by high-fat diet

Authors: *C. WAKABAYASHI, T. NUMAKAWA, Y. OOSHIMA, K. HATTORI, H. KUNUGI;
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Abstract: High-fat diet (HFD) has been recently reported to induce sensorimotor gating deficits, but the underlying mechanisms are not well understood. To determine whether HFD induces long-lasting deficits in sensorimotor gating and to examine the involvement of altered dopamine (DA) function. C57BL/6J mice were fed HFD for 10 weeks and then normal diet (ND) for 4

weeks. DA D2 receptor (D2R) knock out (KO) mice were also fed HFD for 10 weeks. The mice were evaluated for prepulse inhibition (PPI) of acoustic startle after HFD and the subsequent 4-week ND. We evaluated the effect of SCH23390, a D1 receptor (D1R) antagonist, on PPI and measured protein expression levels of D1R and D2R in the prefrontal cortex (PFC) and striatum in HFD mice. The concentrations of monoamines and their metabolites in the cortices of 10-week HFD or ND mice were measured using high performance liquid chromatography. Long term HFD induced PPI disruption in WT and D2R KO mice. Even after 4 weeks of subsequent ND, PPI remained to be disrupted. SCH23390 mitigated the PPI disruption. In HFD animals, D1R protein expression in the PFC was significantly decreased, while DA and its metabolites homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC) levels in the cortex were increased. This is the first evidence that HFD can induce long-lasting deficits in sensorimotor gating through alteration of cortical levels of DA, HVA, and DOPAC. Our data suggest that HFD-induced PPI deficits are related to altered D1R, rather than D2R, signaling and that D1R antagonists may have therapeutic effects on the deficits.

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Poster

785. Monoamines and Behavior: Dopamine and Norepinephrine

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Topic: C.18. Behavioral Pharmacology

Support: Beijing Natural Science Foundation 7133259

National Natural Science Foundation of China 81171284

Title: Prenatal risperidone exposure enhances prepulse inhibition of acoustic startle reflex in adult male mice

Authors: ***Y.-A. SU**[1,2,3], H. WANG[1,2,3], J.-T. LI[1,2,3], T.-M. SI[1,2,3];
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Abstract: Background Psychiatric disorders are relatively common among women of childbearing age. However, the use of antipsychotics during pregnancy remains controversial. The potential embryotoxicity of the antipsychotics has to be weighed against the risk of relapse

following drug discontinuation, and the decision-making must be based on extensive research evidence. Previous animal studies indicate that prenatal exposure to antipsychotics may impair the cognitive function of adult offspring. The current study investigated whether prenatal risperidone treatment would produce long-term effects on behavior in adult male offspring. Methods All plug-positive female C57BL/6 mice were randomized two groups. Pregnant dams of both groups were exposed to risperidone at a dose of 2mg/kg body weight or vehicle (0.9% normal saline) intraperotoneally from embryonic day 6 to 16. The day of delivery was defined as postnatal day 0 (P0). Pups were reared by their biological mothers up to weaning (at P28). Only male mice were used for behavioral observations. On P75, mice were examined in the spontaneous locomotion, spatial object recognition, elevated plus maze and prepulse inhibition (PPI) of acoustic startle reflex sequentially. Results Maternal risperidone exposure from E6 to E16 reduced maternal body weight gain after the first drug administration and showed recovery on subsequent days. The data showed no significant difference in the body weight of treated offspring as compared to those of the controls. The total distance traveled in the novel environment of the open field test did not reveal any differences between two groups. Male mice offspring exposed to risperidone showed deficits in spatial object recognition when compared with control group. However, prenatally risperidone exposed mice displayed less anxiety like behavior in the elevated plus maze. In addition, the offspring of risperidone group showed significantly potentiated PPI; this effect was most striking with the two lowest prepulse intensities. Conclusion The findings of impaired spatial memory, reduced anxiety-like behavior and enhanced prepulse inhibition suggest that prenatal risperidone could produce both negative and positive long-term behavioral changes. The mechanism of risperidone's action on neurodevelopment remains to be clarified.

Disclosures: **Y. Su:** None. **H. Wang:** None. **J. Li:** None. **T. Si:** None.

Poster

785. Monoamines and Behavior: Dopamine and Norepinephrine

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 785.10/K37

Topic: C.18. Behavioral Pharmacology

Support: Grant from Sigrid Juselius Foundation

Title: Tyrosine hydroxylase 2 is involved in the regulation of habituation in adult zebrafish

Authors: ***S. A. SEMENOVA**, Y.-C. CHEN, P. A. J. PANULA;
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Abstract: Zebrafish has two non-allelic tyrosine hydroxylase (TH) genes, of which TH1 is more similar to its mammalian counterparts. The gene encoding tyrosine hydroxylase 2 (TH2) is primarily expressed in the hypothalamus, and the most prominent TH2 neuron groups are found close to the lateral and posterior recesses of the diencephalic ventricle, in the immediate vicinity of adult neurogenesis zones. Apart from the effect of stress on th2 gene expression in larval and adult fish, the regulation of expression of this gene and its functions in the nervous system are not completely characterized yet. We previously developed an antibody against zebrafish TH2 and used it to demonstrate that TH2 neurons of zebrafish are targeted by histaminergic and orexinergic signaling. Serotonergic and TH2 neurons were distinct, although cells of the two phenotypes were intermingled in the hypothalamic nuclei. Morpholino oligonucleotide (MO)-mediated knockdown of th2 gene expression affected the development of histaminergic and orexinergic neurons in larval zebrafish; however, the locomotor behavior of larvae was not significantly altered by MO injection. Handling or chemical stress induced prominent expression of the immediate early gene c-fos in the zebrafish hypothalamus, but very few TH2-immunopositive cells were involved in this acute response. We used the CRISPR/Cas9 approach to generate a mutant zebrafish line with a six-nucleotide deletion in exon 2 of the th2 gene. Adult male heterozygous fish appeared phenotypically normal and were fertile. Open-field behavioral test revealed altered habituation in heterozygous fish; however, changes in spatial preference evident of increased anxiety (thigmotaxis) were not detected. There was a trend towards increased interaction with own mirror image in heterozygous fish. Therefore, a role in modulation of the habituation reaction in adult zebrafish can be assigned to TH2 neurons.

Disclosures: **S.A. Semenova:** None. **Y. Chen:** None. **P.A.J. Panula:** None.

Poster

785. Monoamines and Behavior: Dopamine and Norepinephrine

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Topic: C.18. Behavioral Pharmacology

Support: Brown Institute for Brain Science Innovation Fund

Michael J Fox Foundation

Title: Antipsychotic medications induce sustained alterations in approach/avoidance learning

Authors: *N. E. VIERLING-CLAASSEN[1], A. COLLINS[2], D. BURKE[1], H. WARWICK[1], B. REGO[1], M. HILL[1], K. BATH[2], M. J. FRANK[2], C. I. MOORE[1];
[1]Neurosci., [2]Cognitive, Linguistic and Psychological Sci., Brown Univ., Providence, RI

Abstract: The most common psychiatric treatment for severe mental illness is antipsychotic (APsy) medication. APsy minimize "positive" symptoms of psychiatric disorders, including overt psychosis, but also fail to treat and may increase "negative" symptoms, such as suppressed motivation. This shortcoming is major, as the severity of negative symptoms is predictive of long-term recovery and function. Almost all APsy block 'D2' dopaminergic receptors, increasing the excitability of striatal D2 medium spiny neurons (MSNs) by removing a source of inhibition. D2 blockade leads to suppressed motivation, down regulation of behavior and eventually motor symptoms such as catalepsy. Computational models suggest a common set of interactive mechanisms giving rise to these effects: by disinhibiting the D2 "no-go" corticostriatal pathway, APsy enhance the motivational cost of action and learning from negative reward prediction errors, driving progressive avoidance learning. This combination of mechanisms – with additional interactive effects across ventral and dorsal striatum – provides a recipe for learned avolition and generation of negative symptoms. Most empirical studies focus on either the motivational or instrumental learning components of striatal dopamine function, in some cases confounding the two. We have developed a behavioral paradigm that allows us to separately assess approach/avoidance instrumental learning vs. motivation to engage in the task. Mice are cued to lick in response to the light cue that signals water availability at a single spout. 2-3.5 seconds later, one of two auditory tone cues (4KHz or 11KHz) predicts a switch in tastant delivery from water to either sucrose or quinine at the same spout. Motivation is assessed by response rate to the cue light, whereas instrumental learning is assessed by changes in responding as a function of auditory tone. Control mice (n=3) exhibited distinct responses to the two tones by day 6 (suppression for quinine-paired tone and continuation of licking for the sucrose paired tone), achieving maximum performance at 14 days. Motivation increases across days as indicated by increased trial initiation. We find that haloperidol (n=2 mice, 0.15 mg/kg) and D2 antagonist eticlopride (n=1, 0.16 mg/kg) caused learned lack of motivation while also blocking instrumental learning in response to tones, indicating a dissociation that does not simply amount to reduced behavioral output. Further, this altered behavior persists after drug exposure has ceased. Computational simulations provide alternative testable hypotheses for the mechanisms underlying these effects.

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Poster

785. Monoamines and Behavior: Dopamine and Norepinephrine

Location: Hall A

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Topic: C.18. Behavioral Pharmacology

Support: NIDA T32DA07268

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Michael J Fox Foundation

Title: The effects of acute cocaine administration on striatal monoamine levels in obesity-prone rats

Authors: *P. J. VOLLBRECHT[1], O. S. MABROUK[2], A. D. NELSON[1], R. T. KENNEDY[3], C. R. FERRARIO[1];
[1]Pharmacol., [2]Pharmcology, Chem., [3]Medicinal Chem., Univ. of Michigan, Ann Arbor, MI

Abstract: The current obesity epidemic has hastened the need to understand the neural mechanisms that contribute to over-eating and weight gain. Recent work has emphasized the importance of the mesolimbic reward pathway in aberrant eating behaviors. Enhanced striatal activation is linked to stronger food craving, greater food consumption, and difficulty losing weight in obese people. In addition, decreased striatal D2 receptor binding has been found in obese people, and consumption of fatty foods decreases D2R mRNA expression in rats. However, it is unclear to what extent pre-existing differences in striatal function may contribute. Here, we examined differences in cocaine-evoked locomotion and neurotransmitter levels in the ventral striatum of obesity-prone and -resistant rats without diet manipulation. In addition, sensitivity to the D2R agonist quinpirole was determined prior to and after exposure to a "junk-food" diet. We used microdialysis coupled with LC-MS and utilized a benzoyl chloride derivitization technique to isolate multiple neurochemicals in a single sample with high temporal resolution (3 minutes/sample). Specifically, basal and cocaine-evoked levels of monoamine neurotransmitters (dopamine, norepinephrine, and serotonin), their metabolites, as well as glutamate, GABA, acetylcholine, histamine, glutamine, glycine, aspartate, taurine, serine, adenosine, phenylalanine, glucose, and tyrosine in the ventral striatum were measured alongside locomotor activity. In addition, the inclusion of stable-radiolabeled isotopes also allowed us to calculate basal concentrations of dopamine and glutamate. Basal concentrations of monoamine neurotransmitters did not differ between groups. Consistent with our previous results, cocaine produced a stronger locomotor response in obesity-prone vs. obesity-resistant rats. Cocaine

increased dopamine and serotonin levels similarly in both groups, but resulted in elevations in norepinephrine only in obesity-prone rats. Ongoing studies are examining differences in sensitivity to NET selective blockers. Enhanced cocaine-induced locomotion in obesity-prone rats may be mediated by differences in post-synaptic transmission. Consistent with this, obesity-prone rats were less sensitive to quinpirole. This response was further suppressed by "junk-food" exposure in obesity-prone rats, whereas "junk-food" had less pronounced effects on quinpirole sensitivity in obesity-resistant rats. Together our data show that there are both pre-existing and diet-induced alterations in striatal systems of obesity-prone rats that are distinct from those found in their obesity-resistant counterparts.

Disclosures: P.J. Vollbrecht: None. **O.S. Mabrouk:** None. **A.D. Nelson:** None. **R.T. Kennedy:** None. **C.R. Ferrario:** None.

Poster

785. Monoamines and Behavior: Dopamine and Norepinephrine

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 785.13/K40

Topic: F.03. Motivation and Emotion

Support: EU FP7 Full4Health (266408)

Title: Direct inhibition of ventral tegmental area dopamine neurons decreases reward-seeking behavior

Authors: R. VAN ZESSEN[1], G. VAN DER PLASSE[1], *G. M. RAMAKERS[2], G. D. STUBER[3], R. A. H. ADAN[1];
[1]Translational Neurosci., [2]Brain Ctr. Rudolf Magnus, UMC Utrecht, Utrecht, Netherlands; [3]Psychiatry & Cell Biology. and Physiol., Univ. of North Carolina, Chapel Hill, NC

Abstract: Ventral Tegmental Area (VTA) dopaminergic (DA) neuronal activity plays an important role in behavioral responses to food rewards as well as the environmental cues that predict them. Over the last few years, *in vivo* optogenetic approaches have provided important insights into the involvement of VTA DA neurons during behavior. It has been established that activation of VTA DA neurons promotes behavioral activation and acts reinforcing. In direct contrast, long-term inactivation of these same neurons evokes an aversive phenotype. Although it has also been clearly established that the activity of these neurons encodes a reward-prediction error that is instrumental for associative learning, it has not been directly assessed whether this signal is necessary for reward-seeking behavior. Therefore, we used an *in vivo* optogenetic

approach to manipulate VTA DA neurons in freely moving mice during this behavior. Mice were trained on a cue-reward seeking task, where a five second cue predicted the delivery of a sucrose reward. We then inhibited the activity of VTA DA neurons during cue presentation and during reward retrieval, and found decreases in anticipatory and consumatory responses. In control experiments licking-related locomotor behavior remained unimpaired. We conclude that direct inhibition of VTA DA neurons decreases behavioral performance on cue-reward seeking tasks. We are now exploring the dynamics of associative learning and the specificity of this performance decrease.

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Poster

785. Monoamines and Behavior: Dopamine and Norepinephrine

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Topic: C.18. Behavioral Pharmacology

Support: NeuroBasic

Title: Functional dissociation between rat midbrain dopamine neuron subpopulations in the regulation of locomotor activity

Authors: L. BOEKHOUDT, A. OMRANI, E. C. WIJBRANS, M. C. M. LUIJENDIJK, I. G. WOLTERINK, *G. VAN DER PLASSE, R. A. H. ADAN;
Brain Ctr. Rudolf Magnus, Utrecht, Netherlands

Abstract: Midbrain dopamine neurons are involved in the regulation of various behaviours, ranging from locomotion and reward learning to cognitive functioning. Dysregulation of the dopamine system is associated with a variety of psychopathologies, including addiction, schizophrenia, and attention deficit/hyperactivity disorder (ADHD). However, it remains unknown if, and how, activity of midbrain dopamine neurons is directly linked to the expression of psychiatric symptoms, such as hyperactivity in ADHD. Furthermore, it is currently unidentified how the two main subpopulations of midbrain dopamine neurons, i.e. the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc), are involved in the regulation of hyperactivity. In this study, we used designer receptors exclusively activated by designer drugs (DREADD) to selectively activate midbrain dopamine neurons in either VTA or SNc, and measured the effects on home cage locomotor activity in TH::Cre rats. Activation of both

subpopulations significantly increased locomotor activity. However, whereas chemogenetic activation of SNc dopamine neurons only modestly increased locomotor activity, activation of VTA dopamine neurons induced a pronounced hyperactive phenotype. Pathway specific neuronal activation showed that, although VTA neurons projected to both the ventral and dorsomedial striatum, hyperactivity was primarily caused by VTA projections to the nucleus accumbens. In addition to hyperactivity, we also observed a disturbed feeding pattern following activation of VTA, but not SNc, dopamine neurons. These results show a clear functional dissociation between virally targeted subregions of the dopaminergic midbrain in rats, and suggest that specifically VTA dopamine neurons that project to the nucleus accumbens are involved in the regulation of hyperactive locomotion. Here we show that DREADD technology can be used to effectively manipulate dopamine specific or pathway specific neuronal subpopulations in the rat midbrain, and thereby gain insights into the dopaminergic circuitries that are involved in the regulation of behaviour, and, potentially, psychiatric symptoms.

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Poster

785. Monoamines and Behavior: Dopamine and Norepinephrine

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Support: Israel Ministry of Health Chief Scientist grant

Herman Dana Foundation.

Title: Altered mononuclear cell gene transcriptional reactivity among Methylphenidate responders with Attention Deficit and Hyperactivity Disorder

Authors: *R. SEGMAN[1], T. GOLTSER-DUBNER[2], A. MELTZER[3], G. BODENHEIMER[3], A. SHARON[3], R. GIESSER[3], L. KALMAN[3], A. SHALEV[3], L. CANETTI[2], E. GALILI-WEISSTUB[3];
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Abstract: Background: Understanding of stimulant drug molecular action is mostly limited to animal models due to restricted timely access to relevant neural cells in humans, precluding a focus on the molecular correlates of clinical response to the drug. Methods: Drug naive children with Attention Deficit Hyperactivity Disorder (ADHD) underwent a computerized prospective assessment of medication treatment response. Prospectively documented clinical response was correlated with blood mononuclear cell (BMC) transcriptional changes before and after acute (2 hours) and sub acute (2 weeks) MPH exposure. Results: MPH induced BMC transcriptional alterations correlated with clinical response patterns, implicating molecular targets which may point to mechanistically relevant constructs. Conclusions: Prospectively quantified MPH induced improvements in sustained attention and commission errors reveal coincident short term surrogate mononuclear cell transcriptional reactivity which may point to selective underlying molecular targets of MPH response.

Disclosures: R. Segman: None. **T. Goltser-Dubner:** None. **A. Meltzer:** None. **G. Bodenheimer:** None. **A. Sharon:** None. **R. Giesser:** None. **L. Kalman:** None. **A. Shalev:** None. **L. Canetti:** None. **E. Galili-Weisstub:** None.

Poster

785. Monoamines and Behavior: Dopamine and Norepinephrine

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 785.16/L1

Topic: C.18. Behavioral Pharmacology

Title: Repeated toluene exposure does not increase activation of dopaminergic cells in the nigrostriatal pathway of adolescent mice

Authors: *J. N. LOMBARDO, S. E. BOWEN, M. L. TOMASZYCKI;
Psychology, Wayne State Univ., Detroit, MI

Abstract: Toluene, an industrial chemical found in many consumer products, is often abused for its intoxicating properties. While the neurobehavioral effects of toluene have been well studied, the mechanisms by which abused inhalants exert these effects are not well understood. Since toluene has been shown to act on catecholaminergic cells within the basal ganglia, one area of particular interest is the nigrostriatal pathway. In the present study, adolescent outbred mice (Swiss-Webster; N = 32) were exposed to 0, 1000, 2000, and 4000 ppm toluene for 30 minutes per day for seven consecutive days, after which the animals were sacrificed and brain tissue was collected. The caudate-putamen (CPu) and substantia nigra pars compacta (SNc) were then double-labeled for tyrosine hydroxylase (TH; an enzyme for dopamine synthesis) and c-Fos (a

proxy of neural activity). While none of the toluene exposures resulted in changes in c-Fos or TH expression within the SNc, the highest toluene exposure of 4000 ppm toluene increased the number of cells immunopositive for c-Fos, but not c-Fos + TH, within the CPu. Taken together, these results suggest that the neurobehavioral effects of toluene are exerted through a mechanism other than the dopaminergic nigrostriatal pathway.

Disclosures: J.N. Lombardo: None. **S.E. Bowen:** None. **M.L. Tomaszycki:** None.

Poster

786. Olfaction: Olfactory Bulb

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 786.01/L2

Topic: D.01. Chemical Senses

Support: NIDCD Grant F31DC013490

NIDCD Grant R01DC011184

Pennsylvania Department of Health's Commonwealth Universal Research Enhancement Program

Title: Deep short-axon cells regulate multi-glomerular activation patterns in the mammalian main olfactory bulb

Authors: *S. D. BURTON[1,2], G. LAROCCA[1], A. LIU[2,3], C. E. CHEETHAM[1], N. N. URBAN[1,2,3];
[1]Biol. Sci., Carnegie Mellon Univ., Pittsburgh, PA; [2]Ctr. for the Neural Basis of Cognition, Pittsburgh, PA; [3]Ctr. for Neurosci., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Sensory processing in the vertebrate olfactory system begins with the generation of an odor-specific pattern of glomerular activation across the surface of the main olfactory bulb (MOB). Within each glomerulus, periglomerular cells (PGCs) modulate sensory input by inhibiting sensory axon terminals, glutamatergic external tufted cells (ETCs), and the apical dendrites of principal mitral and tufted cells (M/TCs). Here, we characterize a novel circuit capable of tuning MOB sensory input by regulating interglomerular PGC activity. Specifically, we identify a class of glomerular layer-projecting deep short-axon cells (GL-dSACs) that selectively express nicotinic acetylcholine receptor subunit α2 (*chrna2*) and synaptically inhibit PGCs across multiple glomeruli. Using transgenic Chrna2-Cre mice, we show that GL-dSACs have large somata (mean diameter: 17.0 ± 1.2 μm, μ ± σ, n=6), extend 4.5 ± 1.6 (n=6) dendrites

≤200 μm within the internal plexiform layer (IPL), and project axons through the external plexiform layer (EPL) to arborize across multiple glomeruli. GL-dSACs are immunonegative for markers of EPL-projecting dSACs, and ~50% of Chrna2-Cre-labeled GL-dSACs exhibit strong $GABA_AR\alpha1$ expression. Strikingly, all glomeruli exhibit profuse innervation by GL-dSAC axons that are immunonegative for tyrosine hydroxylase, identifying GL-dSACs as a neurochemically distinct subpopulation of MOB interneurons capable of profoundly influencing glomerular activation. Consistent with such a role, optogenetic activation of GL-dSACs in acute slices bathed in NBQX and AP5 evokes monosynaptic inhibitory postsynaptic currents in PGCs. At rest, GL-dSACs exhibit highly regular spontaneous firing in both whole-cell (8.3 ± 5.6 Hz, n=33) and cell-attached recordings that is independent of spontaneous synaptic activity (5.2 ± 5.2 Hz vs. 6.5 ± 6.3 Hz, pre- vs. post-NBQX/AP5/gabazine application, n=10; p=0.12, paired t-test). Stimulation of sensory axons within individual glomeruli reliably evokes strong (200-800 pA), short-latency (4-7 ms), and short-duration (~15 ms) excitatory postsynaptic currents in GL-dSACs that trigger 1-2 action potentials and reset the spontaneous firing phase. This excitation is reliably recruited at stimulation intensities subthreshold for MC activation, suggesting that sensory input to the MOB evokes high-fidelity disynaptic excitation of GL-dSACs via ETC collaterals in the IPL. Collectively, our results thus support a model in which GL-dSACs provide rhythmic multi-glomerular disinhibitory feedback and are strategically positioned deep within the MOB to potentially integrate both intrabulbar and centrifugal input.

Disclosures: S.D. Burton: None. **G. LaRocca:** None. **A. Liu:** None. **C.E. Cheetham:** None. **N.N. Urban:** None.

Poster

786. Olfaction: Olfactory Bulb

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 786.02/L3

Topic: D.01. Chemical Senses

Support: NIDCD grant R01 DC 00997701-06

NINDS grant NS11613

Title: Multistage information processing in the olfactory bulb: role of microcircuits in the glomerular and mitral cells layers for disambiguation of odorant inputs

Authors: *M. MIGLIORE[1,2], F. CAVARRETTA[2,3], A. MARASCO[4], M. L. HINES[2], G. M. SHEPHERD[2];

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Abstract: The olfactory bulb is directly connected to cortical areas, allowing an immediate relay of odor inputs for quick and reliable recognition. Its functions presumably requires highly efficient and exquisitely evolved circuits, to ensure that the information conveyed by the olfactory receptor neurons (ORNs) is cleaned and organized before it reaches the olfactory cortex. The glomerular (GL) and external plexiform (EPL) layers appear to be crucial locations to implement these functions, but their relative role is not yet understood. Using a full scale 3D computational model of the olfactory bulb (Migliore et al., 2014), taking into account several experimental findings for mitral and granule cell interactions, we have explored the basic circuits in the EPL (Migliore et al., 2015), showing the mechanisms for forming one or more glomerular units (a spatially segregated column of granule cell located below a glomerulus and with strong dendrodendritic synapses) in response to a given odor; how and to what extent the glomerular units interfere or interact with each other during learning; their computational role within the olfactory bulb microcircuit; and how their action can be formalized into a theoretical framework in which the olfactory bulb can be considered to contain “odor operators” unique to each individual. Here, we study the relative role for information processing in the olfactory bulb of 1) the inter- and intra-glomerular circuits, modulating olfactory sensory neuron inputs through the combined action of tufted and juxtaglomerular cells in the glomerular layer, and 2) the external plexiform layer circuits, acting on the output stage of the olfactory bulb through the interaction between granule and mitral cell. We found that glomerular level circuits are instrumental in transforming a potentially complex and disorganized sensory input into a contrast enhanced and normalized version, dynamically optimized to be processed and organized by the EPL circuits in terms of glomerular units that could be characteristically associated with individual odorants; EPL circuits further simplify and structure synchronized ensemble of mitral cells that appear to be optimized to code for input odors identity and concentration. This layered organization is especially important for natural odor inputs, which activate many overlapping glomeruli.
References Migliore M, Cavarretta F, Hines ML, Shepherd GM (2014) Front. Comput. Neurosci. 8:50. Migliore M, Cavarretta F, Marasco A, Tulumello E, Hines ML, Shepherd GM, (2015) Proc. Nat. Acad. Sci. USA, in press.

Disclosures: **M. Migliore:** None. **F. Cavarretta:** None. **A. Marasco:** None. **M.L. Hines:** None. **G.M. Shepherd:** None.

Poster

786. Olfaction: Olfactory Bulb

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Program#/Poster#: 786.03/L4

Topic: D.01. Chemical Senses

Support: NSF CMMI - 1435358

Title: Subthreshold oscillations, synchronization, and transitions between rhythms in an olfactory model

Authors: A. KARAMCHANDANI, J. N. GRAHAM, H. MENG, *H. RIECKE;
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Abstract: LFP recordings from the rat olfactory system show activity in β- or γ-bands (15-40 Hz and 50-100 Hz, respectively) following odor presentation. The faster γ-rhythm is generated within the olfactory bulb alone by the interplay of mitral/tufted and granule cells, while the slower β-rhythm requires the interconnectivity of the bulb with piriform cortex, most likely involving pyramidal cells. We aim to elucidate these two rhythms focusing on the role of the characteristic sub-threshold oscillations (STOs) exhibited by the mitral/tufted cells and of the two recurrent pathways involved, one within the bulb and one that also involves cortex. To investigate the role of the STOs and the dual recurrent pathways we introduce a minimal model in which the interactions between the three populations is reduced to an effective inhibitory pulse-coupling within a single population of mitral/tufted cells. The dual pathways are modeled with two types of pulses differing in their delays. The STOs arise from persistent sodium and slow potassium currents included in the Hodgkin-Huxley model. For weak coupling we reduce the system to a stochastic phase model in which the STOs are reflected in the complex interaction between the phase oscillators. For large networks with all-to-all coupling, further reduction leads to a population description in terms of a non-linear Fokker-Planck equation. We find various states differing in the clustering of the oscillator phases. For long delays, corresponding to the cortical pathway, a one-cluster state, representing nearly synchronized oscillators, dominates. For shorter delays, reflecting the intra-bulbar pathway, only states with multiple clusters and higher frequency of the population rhythm arise, resembling a γ-rhythm. In contrast to the PING mechanism for the γ-rhythm of simply spiking excitatory and inhibitory cells, where the population frequency decreases continuously with increasing propagation delay, in our model changes in the delay induce discrete transitions between the different rhythms and the population frequency of the rhythms can increase with increasing delay. We compare these theoretical results with direct numerical simulations of the single-population, spiking-neuron model, extending the results also to stronger coupling.

Disclosures: A. Karamchandani: None. **J.N. Graham:** None. **H. Meng:** None. **H. Riecke:** None.

Poster

786. Olfaction: Olfactory Bulb

Location: Hall A

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Program#/Poster#: 786.04/L5

Topic: D.01. Chemical Senses

Support: NIDCD R01 DC014367

Title: Gamma and beta oscillations in the rat olfactory bulb define a cognitive sequence in odor discrimination

Authors: D. E. FREDERICK[1,2], *L. M. KAY[1,2];
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Abstract: Gamma and beta oscillations of the local field potential (LFP) in rat and mouse olfactory systems have been associated with odor detection, discrimination and learning across a wide array of behavioral tasks within and across laboratories. Gamma oscillations and their analogs in insect systems are local phenomena, supported by the reciprocal dendrodendritic synapse between olfactory bulb (OB) granule cells and mitral/tufted cells, have been associated with discrimination of similar odors across phyla (specifically, rodents and insects). Beta oscillations require intact centrifugal input to the OB and have been linked to learning in go/no-go (GNG) tasks, and gamma oscillations have been identified as the predominant feature in a 2-alternative choice task. We tested the hypothesis that the different tasks engage either gamma or beta oscillations in rats trained in parallel to do either or both tasks. We used many different odor sets that span several orders of magnitude in theoretical vapor pressure and degrees of similarity between components to be discriminated. We show that both gamma and beta oscillations are represented in both tasks. Gamma oscillations dominate in the first 2-3 sniffs after the rat begins odor sampling, and beta oscillations begin after 200 msec of odor sampling. If rats do not sniff long enough to engage the beta oscillation mode, their performance on odor discrimination is above chance. If they sample longer, their performance improves. We falsify our hypothesis and show that task differences are a matter of degree, with oscillations of all types stronger in the GNG task during odor sampling. We also show that very fast OB gamma oscillations (~90 Hz), presumed to be associated with tufted cells, dominate early in odor sampling (first 2-3 sniffs), and that lower frequency gamma oscillations (~70 Hz), presumed to be associated with mitral cells, dominate during the later part of odor sampling (>200 msec of odor sampling). These results, combined with earlier results, suggest that this early olfactory processing network is strongly modulated by the context of the odor discrimination and the manner in which the animals are trained. However, we also show that gamma and beta oscillations, when they are

present, maintain a stable temporal relationship to odor sampling behavior and identify early and late cognitive processes in odor discrimination and identification.

Disclosures: D.E. Frederick: None. **L.M. Kay:** None.

Poster

786. Olfaction: Olfactory Bulb

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 786.05/L6

Topic: D.01. Chemical Senses

Support: NIDCD R01 DC014367

Title: Granule cell excitability mediates gamma and beta oscillations in a model of the dendrodendritic microcircuit

Authors: *B. L. OSINSKI, L. M. KAY;
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Abstract: Odors evoke gamma (60 - 100 Hz) and beta (20 - 30 Hz) oscillations in the local field potential (LFP) of the rat olfactory bulb (OB). These oscillations arise from activity in the dendrodendritic microcircuit between excitatory mitral cells (MCs) and inhibitory granule cells (GCs). When cortical feedback inputs to the OB are blocked, beta oscillations are extinguished while gamma oscillations persist. Much of this cortical feedback targets inhibitory interneurons in the GC layer and regulates the excitability of GCs, which suggests a causal link between the emergence of beta oscillations and the GC excitability. GC dendritic spines are known to express N-methyl-D-aspartate receptors (NMDARs) and voltage-dependent calcium channels (VDCCs), both of which are sensitive to changes in GC excitability and can mediate graded inhibition onto MCs. In a biophysical model of the MC-GC dendrodendritic network we investigate how the network oscillations driven by NMDAR and VDCC mediated graded inhibition of MCs depend on GC excitability. When GC excitability is low, there is transient activation of NMDARs and VDCCs by AMPARs, which produces fast inhibitory pulses in the gamma frequency range. When GC excitability is increased, the activation of NMDARs and VDCCs is prolonged, allowing the slow decay time constants of these channels to drive beta frequency oscillations. While both NMDARs and VDCCs can drive gamma and beta oscillations, the power of beta oscillations is much higher when VDCCs alone are used. This suggests that the high power beta oscillations that have been experimentally recorded are more dependent on calcium flow through VDCCs than NMDARs.

Disclosures: **B.L. Osinski:** None. **L.M. Kay:** None.

Poster

786. Olfaction: Olfactory Bulb

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Topic: D.01. Chemical Senses

Support: MBL Neurobiology Course

NIDCD RO1-DC-009817 to R.C.A.

Title: Hyperpolarization-activated currents and subthreshold resonance in granule cells of the olfactory bulb

Authors: *R. HU[1,2], K. A. FERGUSON[3], C. B. WHITEUS[3], D. H. MEIJER[3], R. C. ARANEDA[1,2];
[1]Biol., Univ. of Maryland, College Park, MD; [2]Neurosci. and Cognitive Sci. Program, College Park, MD; [3]Marine Biol. Lab., Woods Hole, MA

Abstract: In sensory systems, neural circuits exhibit oscillatory dynamics driven by sensory input, extrinsic regulation, and intrinsic circuit properties. Activation and inactivation of currents, such as hyperpolarization-activated currents (I_h), are involved in generating membrane potential oscillations in neurons and contribute to network oscillatory dynamics. In the olfactory system, initial processing of odor signals occurs in the olfactory bulb (OB) and an important aspect of this processing, network synchrony, arises from the activity of reciprocal synapses between output neurons, the mitral and tufted cells (MCs herein), and inhibitory interneurons, the granule cells (GCs). Interestingly, MCs exhibit varying expression of I_h, suggesting a contribution of this current to the fidelity of information coding by MCs. In contrast, the presence of I_h in the GC population is poorly characterized. Here, using patch-clamp recordings, we show that GCs in the main OB (MOB) and accessory OB (AOB) exhibit I_h. Although maximal current for I_h varied across cells, voltage dependency was consistent in both regions (MOB: V_{half} = -105 ± 4 mV, n = 7; AOB: V_{half} = -99 ± 3 mV, n = 9). In addition, I_h in AOB and MOB GCs showed a similar sensitivity to changes in extracellular K^+ concentration, and blockage by ZD-7288 (30μM). However, loading the intracellular pipette solution with cAMP (500μM) shifted the activation curve of I_h to less negative potentials in GCs in the MOB, but not the AOB (MOB: V_{half} = -94 ± 3 mV, n =8; AOB: V_{half} = -96 ± 4 mV, n = 6). When applying the standard impedance amplitude (ZAP) protocol, we found heterogeneity across AOB and MOB

GCs in subthreshold resonance properties, with resonant cells (16/42 GCs) having resonant frequencies in the delta (1-4Hz) range. This subthreshold resonance phenotype is mediated by I_h and can be abolished by application of ZD7288. When comparing resonant and non-resonant GCs, resonant neurons tend to have lower input resistance (resonant cell mean input resistance = 1.04 ± 0.10 GΩ, non-resonant cell mean input resistance = 1.58 ± 0.15 GΩ) and larger I_h (resonant cell mean I_{max} = -176 ± 26 pA, non-resonant cell mean I_{max} = -103 ± 21 pA). These results suggest the expression of I_h and subthreshold resonance in GCs may impart unique features to odor processing in the OB and facilitate oscillatory dynamics in both the main olfactory and Vomeronasal systems.

Disclosures: R. Hu: None. **K.A. Ferguson:** None. **C.B. Whiteus:** None. **D.H. Meijer:** None. **R.C. Araneda:** None.

Poster

786. Olfaction: Olfactory Bulb

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 786.07/L8

Topic: D.01. Chemical Senses

Support: NIH-NIDCD DC 009817

Title: Inhibition of granule cells by adult born neurons in the olfactory bulb

Authors: P. S. VILLAR[1], A. NUNEZ-PARRA[2], K. KRAHE[1], C. EBERLY[1], *R. C. ARANEDA[1];
[1]Univ. of Maryland, College Park, MD; [2]Anschutz Med. Ctr., Univ. of Colorado, Denver, CO

Abstract: In the adult brain, thousands of newly born neurons arrive every day into the olfactory bulb (OB). These adult born inhibitory neurons, mostly granule cells (GCs), produce a continuous remodeling of the pre-existing circuits forming new synapses with other inhibitory neurons and with the main output neurons of the OB, the mitral cells (MCs). In the adults, the accessory olfactory system plays a crucial role in the expression of behaviors such as aggression and mating. Here we study the properties and functional role of newly form inhibitory synapses generated by the postnatal arrival of interneurons into in the adult accessory olfactory bulb circuit. Under voltage clamp and using low Cl internal solution GCs exhibited a low occurrence of spontaneous inhibitory postsynaptic currents (sIPSCs) (0.31 ± 0.08 Hz; n=12). In the presence of glutamate receptor blockers (APV, 100 µM; CNQX, 10 µM; LY357385 100 µM) and TTX (1 µM) the frequency of IPSCs (mIPSCs) was not significantly different (0.25± 0.04 Hz; n=12;

p>0.05). The sIPSCs were completely abolished in the presence of the GABAA receptor blocker Gabazine (10 μM). Adult born inhibitory neurons were labeled using injections of a flexed channelrhodopsin (ChR) virus in the rostral migratory stream of GAD2-Cre mice. Thirty days post-injection, LED stimulation (LEDStim) of ChR expressing neurons produced a consistent inhibition on MC's firing (control, 4.2 ± 0.8 Hz; LEDStim, 1.2 ± 0.5 Hz; n=6; P< 0.02) indicating functional integration of GCs. Under voltage-clamp, minimal LEDStim produced large evoked inhibitory postsynaptic currents (eIPSCs) in GCs (117.3 ± 15.9 pA) with a fast rise time (1.3 ± 0.0 ms) and slow decay (50.4 ± 0.0 ms). We further characterized the strength of these synapses using paired pulse LEDStim. Under control conditions the paired pulse ratio (PPR) was 0.44 ± 0.07, (n=6) and this value was increased by decreasing the extracellular Ca2+ concentration from 2 to 0.5 mM (PPR 2.2 ± 0.4). Together these results suggest that GABA release at these synapses exhibited depression. Furthermore, activation of the metabotropic GABABR with baclofen (50 μM) decreased the eIPSC amplitude (control 117.3 ± 15.9 pA; baclofen, 28 ± 4 pA) and also increased the PPR (2.2 ± 0.1; n=2). Similarly, baclofen significantly reduced the frequency of sIPSC (control 0.29 ± 0.05 Hz; baclofen 0.16 ± 0.026 Hz; p<0.002; n=6) and mIPSCs (control, 0.18 ± 0.01 Hz; 0.10 ± 0.01 Hz; p<0.02; n=6). Together these results suggest a high probability of GABA release at these synapses and a presynaptic regulation mediated by GABAB receptors.

Disclosures: P.S. Villar: None. **A. Nunez-Parra:** None. **K. Krahe:** None. **C. Eberly:** None. **R.C. Araneda:** None.

Poster

786. Olfaction: Olfactory Bulb

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 786.08/L9

Topic: D.01. Chemical Senses

Support: Telethon GGP 11116A

Title: OPHN1 regulates the migration of newly generated cells in the olfactory system

Authors: A. MASET[1], L. GALLA[1], *C. LODOVICHI[2];
[1]Venetian Inst. of Mol. Med., Padova, Italy; [2]Neurosci. Inst. CNR, Neurosci. Inst. CNR and Fondazione Ricerca, Padova, Italy

Abstract: Oligophrenin1 (OPHN1), a X-linked gene associated to intellectual disability, encodes a Rho-GTPase activating protein that plays a role in the conformational rearrangements of actin

stress fibers involved in several developmental processes including axon outgrowth, dendritic maturation and cell migration. How these cellular events can affect neuronal wiring and information processing, leading to cognitive disabilities, remain to be understood. To address these questions we analyzed circuit formation and function in the olfactory system (OS) of OPHN1 ko mice. The OS is one of the few neurogenic niches in the adult mammalian brain. Everyday thousands of new neurons generated in the subventricular zone (SVZ) migrate through the rostral migratory stream (RMS) to reach the olfactory bulb (OB) where they become mature interneurons, i.e. granule cells (GCs). Using bromodeoxyuridine (BrdU), as a cell division marker we found that the number of new cells generated in the SVZ was similar in control and OPHN1 ko mice, 24 hours post injection. However the amount of new cells that reached the OB was significantly reduced in of OPHN1 ko mice, 15 days after BrdU injection. To assess whether mutation in OPHN1 could affect the migration of the new cells, we analyzed the migration process from the SVZ to the OB, in sagittal sections of the brain using double cortin (DCX), a marker of neuronal precursors and BrdU. We found that the spatial organization of neuronal precursors around the SVZ and along the RMS was deeply perturbed in OPHN1 ko mice. The new cells were not arrange in chains but tended to coalesce in clumps. Using lentiviral expressing GFP and immunostaining for DCX, we found that both the polarity and the direction of migration of the cells were strikingly disrupted in OPHN1 ko mice, respect to controls. All together our data demonstrated that the migration of adult generated cells is deeply affected in OPHN1 ko mice, resulting in a strikingly reduction of new GCs in the OB of OPHN1 ko mice. We are currently investigating how such a strikingly reduction in adult generated interneurons can affect circuit function in the olfactory bulb.

Disclosures: **A. Maset:** None. **L. Galla:** None. **C. Lodovichi:** None.

Poster

786. Olfaction: Olfactory Bulb

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 786.09/L10

Topic: D.01. Chemical Senses

Support: Graduate School of Cellular and Molecular Neuroscience, Tübingen

Title: Distinct physiological properties of mature adult-born neurons in the olfactory bulb of awake mice

Authors: N. FOMIN, S. FINK, Y. KOVALCHUK, Y. LIANG, *O. GARASCHUK;
Univ. of Tübingen, Physiol. 2, Tübingen, Germany

Abstract: Mammalian olfactory bulb (OB) is continuously supplied with adult-born neurons (ABCs). *In vivo* cell-attached recordings in anesthetized mice suggest that ABCs acquire odor response properties similar to that of resident cells (RCs) by 8-9 weeks of age. The odor response properties of these cells in awake animals as well as their spiking properties at rest remain, however, unclear. Here we use *in vivo* two-photon calcium imaging to study the properties of mature ABCs (mABCs, 8-19-week-old) in awake, head-restrained mice. We labeled the cells with the ratiometric FRET-based Ca2+-indicator Twitch-2B. To label mABCs, the indicator was injected into the RMS of 2-6-month-old mice, whereas RCs were labeled by direct injections into the OB of 3-4-week-old mice. In awake mice mABC's YFP/CFP ratios, which are proportional to basal Ca2+-levels, ranged from 1.7 to 5.9 (median: 2.7, interquartile range (IQR): 2.3-3.3; n=68 cells in 5 mice). Blocking action potential firing with tetrodotoxin reduced the ratios below 2, suggesting that cells with ratios above 2 (here, 93% of all mABCs) are continuously spiking. In contrast, 100% of RCs (more than 25-39-week-old) were continuously spiking in awake mice. Moreover, RCs had significantly higher YFP/CFP ratios (median: 3.6, IQR: 3.0-4.1, n=140 cells in 5 mice), indicative of the higher spiking frequencies of these cells. Odor stimulation (ethyl-tiglate, 1.67% of saturated vapor) evoked larger responses in mABCs (median amplitude: 168.13, IQR: 118.94-270.38 % ΔR/R) compared to RCs (median amplitude: 107.58, IQR: 80.03-165.74 % ΔR/R). The response variability (coefficient of variation) was significantly higher for mABCs compared to RCs. Under anesthesia, the median basal YFP/CFP ratio dropped significantly in both groups of cells (mABCs: 1.9, IQR: 1.8-2.2; RCs: 3.0, IQR: 2.5-3.6), but the fraction of continuously spiking RCs remained unchanged (98%). In contrast, we observed a significant reduction in the fraction of continuously spiking mABCs (from 93% in awake to 53% in anesthetized mice). In addition, anesthesia caused a significant increase in the median response amplitude (mABCs: 265.07, IQR: 140.02-360.85 % ΔR/R; RCs: 134.96, IQR: 90.96-174.17 % ΔR/R) and a significant decrease in the response variability for both groups of cells. Thus, long after the integration of mABCs into the OB network they still can be distinguished from RCs based on 1) lower basal Ca2+-levels and lower fraction of spiking cells, 2) higher amplitudes of odor-evoked responses 3) higher response variability in awake state and 4) a significant decrease in the fraction of continuously spiking cells under the anesthesia.

Disclosures: **N. Fomin:** None. **S. Fink:** None. **Y. Kovalchuk:** None. **Y. Liang:** None. **O. Garaschuk:** None.

Poster

786. Olfaction: Olfactory Bulb

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Program#/Poster#: 786.10/L11

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NIDCD/NIH Grant R00DC011780

Title: Noradrenergic modulation of information processing in the male accessory olfactory bulb

Authors: *W. I. DOYLE[1,2], J. P. MEEKS[1,2];
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Abstract: In many terrestrial mammals, the accessory olfactory system (AOS) is an olfactory system involved in the sensing and interpretation of non-volatile odorants. The first site of information processing in the AOS is the accessory olfactory bulb (AOB), a small brain region that processes incoming sensory signals from the vomeronasal organ and is also innervated by centrifugal fibers originating in the locus coeruleus. Noradrenaline (NA) is released from these projections, and is hypothesized to play important roles in AOB function. In this study we have examined the effects of NA on information processing by AOB principal neurons in *ex vivo* preparations of the male C57BL/6 and B6D2F1 AOS. This preparation allows us to study the actions of NA in the AOB in the context of carefully controlled peripheral vomeronasal stimulation with odorants. We measured neuronal responses to various vomeronasal odorants before, during, and after application of 10 μM NA. We observed many neurons that underwent significant odorant suppression following NA administration. Significant suppression was seen in responses to 7/19 (37%) of stimuli during NA application, compared to 2/17 (12%) of stimulus responses during vehicle controls ($p < 0.01$). This selective increase in the frequency of observed odorant response suppression indicates that NA-mediated inhibition does not result in global inhibition. Further support for this conclusion was gleaned from measurements of spontaneous spiking activity, which was not significantly decreased following NA application. Overall, these data suggest that NA may not act as a global source of activity suppression in the AOB, but instead may have more subtle and nuanced actions on information processing.

Disclosures: W.I. Doyle: None. **J.P. Meeks:** None.

Poster

786. Olfaction: Olfactory Bulb

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Title: Imaging olfactory bulb plasticity during olfactory experience

Authors: *M. W. CHU, T. KOMIYAMA;
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Abstract: Recent studies suggest an intriguing role for the olfactory bulb as more than just a relay station from the nose to the brain: it is a place where the early processing of odor information can be modulated by experience, behavioral state and odor context, which in turn, affects olfactory perception. Here, we explore long-term changes in mitral cell odor representations in mice during two types of olfactory experience which have been shown to result in perceptual learning: passive experience, where mice are passively and repeatedly exposed to two very similar odors, and active learning, where mice are engaged in a task to discriminate between the same, two similar odors. The activity of mitral cell populations are monitored over days of these experience paradigms in awake mice using chronic 2-photon calcium imaging (Kato et al., 2012). During both types of experience, we observe a gradual sparsening in mitral cell odor responses to both odors. Furthermore, experience leads to an enhancement in the discriminability the experienced odors by mitral cell ensembles, and this enhancement is more pronounced with active learning compared to passive exposure. These results support the olfactory bulb as an important locus for olfactory perceptual learning.

Disclosures: M.W. Chu: None. **T. Komiyama:** None.

Poster

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Title: Neuronal mechanisms underlying mating-induced pheromonal memory in the female mouse

Authors: *Y. GAO, C. H. BUDLONG, I. G. DAVISON;
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Abstract: Social interactions are often the source of powerful and enduring memories. In female mice, reproductive encounters drive long-lasting chemosensory imprinting in the accessory olfactory bulb (AOB), altering neural and endocrine responses to the stud male's pheromones. While changes in inhibition are strongly implicated, direct synaptic measurements of AOB plasticity remain lacking. We used whole cell recordings in acute brain slices from recently mated females to examine how mating affects inhibitory microcircuits in the AOB. Spontaneous GABA release onto AOB mitral cells (MCs) was nearly two-fold higher than in sensory-exposed or naïve controls. Mating also modulated synaptic input to AOB interneurons, increasing both the amplitude and frequency of excitatory potentials in granule cells (GCs), the presumed source of MC self-inhibition. Unexpectedly, we found that mating also strongly affected neural excitability, depolarizing GC resting membrane potential by nearly 10 mV. Finally, we tested how the firing of AOB output neurons is affected by reproductive experience. In mated females, many MCs showed strongly reduced firing when tested with repetitive stimulation to mimic repeated behavioral encounters. To investigate how plasticity correlates with neurons encoding stud male pheromones, we made targeted recordings of MCs using activity-dependent GFP labeling. Mating drove robust Fos-GFP expression in a restricted subset of MCs, whose firing rates progressively decreased to less than half that of unlabeled cells, whose responses remained stable. Taken together, our data suggest that pheromonal learning dynamically regulates the output of specific groups of AOB MCs in a way that depends on cumulative past activity. Both synaptic and intrinsic plasticity are likely to underlie mating-induced memory formation.

Disclosures: Y. Gao: None. **C.H. Budlong:** None. **I.G. Davison:** None.

Poster

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Support: ISF GRANT 1075/11

Title: Functional plasticity in the mouse olfactory bulb following motherhood

Authors: Y. SHLOMAI[1], A. VINOGRAD[1], D. MUKHERJEE[1], G. YUAN[2], A. CITRI[1], I. DAVISON[2], *A. MIZRAHI[1];
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Abstract: Motherhood is a dramatic event common across the mammalian line of descent. Motherhood is accompanied by new maternal behaviors aimed at insuring the wellbeing and survival of the offspring. Maternal behaviors are most likely associated with how specific neuronal circuits process information, but these are not well characterized. Here, we studied the functional changes in the olfactory system in mothers, focusing on the main olfactory bulb (OB) of mice. Using *in vivo* two-photon calcium imaging we show that the output of mitral cells (MCs) becomes sparse in mothers resulting in increased odor selectivity. MCs in mothers also show increased delayed temporal patterns of response. Gene profiling and slice electrophysiology show that maternal changes in MCs result from an increased inhibitory drive. To track the mechanism of circuit changes we tested two interneuron populations, parvalbumin expressing (PV) and dopaminergic interneurons. PV-expressing inhibitory interneurons but not dopaminergic neurons show more odor-evoked responses in mothers as compared to virgin mice identifying the PV neurons as a site of plasticity contributing to MCs sparsening. Moreover, MCs changes are long lasting and could be induced, in part, by the mere experience with the pups. The functional plasticity in the OB of mothers provides a novel substrate for understanding odor coding and plasticity during the maternal state.

Disclosures: Y. Shlomai: None. **A. Vinograd:** None. **D. Mukherjee:** None. **G. Yuan:** None. **A. Citri:** None. **I. Davison:** None. **A. Mizrahi:** None.

Poster

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Support: Marie Curie Actions International Incoming Fellowships (n° 625996)

The Swiss National Science Foundation

Title: Ensemble plasticity of odor representation in populations of olfactory bulb output neurons

Authors: *Y. YAMADA[1], K. BHAUKAURALLY[1], I. RODRIGUEZ[2], A. CARLETON[1]; [1]Dept. of Basic Neurosciences, [2]Dept. of Genet. and Evolution, Univ. of Geneva, Geneva, Switzerland

Abstract: In the olfactory system, sensory neurons project their axons in a receptor-specific manner onto olfactory bulb (OB) glomeruli. At this level, sensory neurons release glutamate upon activation and excite OB output neurons (mitral and tufted cells, MCs & TCs, respectively). Odorants are known to recruit a combination of glomeruli, further evoking complex firing patterns in the population of MCs and TCs. While sensory experience can trigger functional plasticity in primary sensory neurons of the olfactory system, it remains unclear whether odor representations in output neurons are plastic. Here we performed chronic two-photon imaging in awake head-fixed mice specifically expressing the genetically encoded calcium indicators GCaMP3/GCaMP6s in MCs and TCs. We monitored fluorescence changes in response to odor applications in individual neurons, and observed either increase or decrease in fluorescence during and after odor application in both populations of output neurons. The decrease of fluorescence is consistent with a decrease of firing rate observed with electrophysiological recordings. Interestingly, repetitive odorant application over several consecutive days altered the odor representation in MCs and TCs of passively exposed animals. We observed weakening in amplitude of both excitatory and inhibitory responses. In summary, our data supports the notion that sensory experience induces ensemble plasticity in OB output neurons. Future experiments will be needed to assess whether similar ensemble plasticity may take place during olfactory discrimination learning tasks.

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Poster

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Topic: D.01. Chemical Senses

Support: NIH DC 011137

Title: Plasticity of mitral cell dendritic morphology in the adult zebrafish olfactory bulb following chemical deafferentation

Authors: *J. M. DICKENS, C. A. BYRD-JACOBS;
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Abstract: Repeated chemical ablation of the olfactory epithelium of adult zebrafish results in the disruption of afferent input to the olfactory bulb, causing a decrease in bulbar volume. To study this effect on a cellular level, we examined the morphology of mitral cells, the primary output neurons of the olfactory bulb. The dendritic processes and arbors of neurons are complex structures, with both their shape and synaptic connections necessary for the maintenance of neuronal structure and function. Afferent/target interactions that maintain dendritic morphology in the adult brain are not yet well understood. The hypothesis of this study was that chronic treatment of the olfactory organ with the detergent Triton X-100 would decrease the complexity of the dendritic arbors of mitral cells within the olfactory bulb. The olfactory epithelium of male and female adult fish was chronically ablated with Triton X-100 every three days for eight weeks, and mitral cells were identified using retrograde tract tracing with a fluorescent dextran applied to whole brains in culture. Unidendritic mitral cells of olfactory bulbs from unoperated control and Triton X-100-treated fish were imaged using whole-mount confocal microscopy. Dendritic length, number of dendritic tips, and dendritic tuft sizes were analyzed from five mitral cells per olfactory bulb of each fish, with five fish in the control and lesioned groups. Dendritic morphology of deafferented cells was notably affected by loss of afferent input. There was a significant difference between the total branch length of control cells and deafferented cells, with an average total length of 373.0±25.67 μm in control cells and 181.7±8.480 μm in deafferented cells ($P<0.0001$). The length of the longest dendrite of each cell was significantly shorter in deafferented cells (49.84±2.094 μm) compared to control cells (78.34±6.278 μm; $P<0.0001$). There were fewer dendritic tips in deafferented cells (9.120±0.5953) compared to control cells (14.64±0.9414; $P<0.0001$). Dendritic tuft area was significantly decreased in deafferented cells (878.0±66.67 μm^2) compared to control cells (2309±258.6 μm^2; $P<0.0001$). These results are similar to those seen following permanent removal of afferent input. Thus, afferent innervation is critical for maintenance of mitral cell dendritic morphology in the adult zebrafish. This study provides a reversible deafferentation model that will allow for future studies of dendritic plasticity following reinnervation and the potential for recovery of output neurons in the adult brain following loss of sensory input.

Disclosures: J.M. Dickens: None. **C.A. Byrd-Jacobs:** None.

Poster

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Support: NICHD Intramural Grant

Title: Coding of plume dynamics in the insect olfactory system

Authors: *Z. N. ALDWORTH, M. A. STOPFER;
NIH-NICHD, Bethesda, MD

Abstract: Oscillatory synchronous activity among populations of neurons, which has been observed in diverse sensory modalities and animal phyla, has been proposed as a mechanism underlying the sparse firing of neurons. Here we investigate the roles of oscillatory dynamics in generating responses to complex odor plumes. The relatively simple olfactory system of the locust provides a useful model for investigating this mechanism. In the locust antennal lobe, odor-driven reciprocal interactions between excitatory projection neurons (PNs) and inhibitory local neurons organize PN spiking into oscillatory synchrony, and the resulting dense, rhythmic waves of spikes are transmitted to the Kenyon Cells (KCs). The KCs transform this temporally patterned, high spike rate input into a broadly distributed, very sparse format: only a small percentage of the KC population fires in response to an odor stimulus, and responsive KCs fire very few spikes. The extreme sparseness of the KC response is believed to result from two factors, membrane conductances that provide a high firing threshold, and feedback inhibition. Precisely synchronized input from PNs is thought to be necessary to overcome these factors to generate sparse and specific spiking in KCs (Perez-Orive et al, 2002). However, when trains of brief pulses of odorant, like those found in odor plumes, are delivered, some of the highest spike rates in KCs are observed during specific plume features when PN oscillatory synchrony is minimal (Brown et al, 2005). The appearance of these spikes is correlated with two forms of plasticity, sensory adaptation in olfactory receptor neurons (Ito et al, 2009), and facilitatory “fast learning” in the antennal lobe (Stopfer and Laurent, 1999; Bazhenov et al, 2006). We propose that interplay between these forms of plasticity leads to a feed-forward mechanism for driving KC firing in the absence of oscillations, thus encoding certain plume features. To test this we are making intracellular and extracellular recordings from PNs and KCs while delivering temporally varying, plume-like pulses of odor. We analyze these recordings by developing generalized linear models of both populations of neurons. Comparing predicted firing rates of the models while changing plasticity parameters will reveal the extent to which adapting and facilitating mechanisms contribute to the encoding of odor plumes.

Disclosures: Z.N. Aldworth: None. **M.A. Stopfer:** None.

Poster

786. Olfaction: Olfactory Bulb

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Topic: D.01. Chemical Senses

Support: KL 762/5-1

KL 762/6-1

Title: Calcium dynamics of antennal lobe local interneurons during olfactory informatiom processing

Authors: *D. FUSCA, A. PIPPOW, P. KLOPPENBURG;
Univ. of Cologne, Biocenter, Cologne, Germany

Abstract: The antennal lobe of insects constitutes the first synaptic relay and processing center of olfactory information, received from olfactory sensory neurons located on the antennae. Complex synaptic connectivity between olfactory neurons of the antennal lobe ultimately determines the spatial and temporal tuning profile of (output) projection neurons to odors. These interactions are mediated by a complex network of inhibitory and excitatory local interneurons (LNs). In the cockroach antennal lobe, we can discriminate two main LN types with distinctive physiological and morphological features: 1) Multiglomerular type I LNs generate sodium driven action potentials upon odor stimulation and exhibit GABA-like immunoreactivity. 2) Type II LNs, in which odor stimulation evokes depolarizations but no sodium driven action potentials do not express voltage dependent transient sodium currents and accordingly do not generate sodium driven action potentials. These LNs are omniglomerular and partly exhibit ChAT-like immunoreactivity (J Neurosci 29(3):716-726 (2009); J Comp Neurol 521(15):3556-3569 (2013)). The distinctive morphological and physiological characteristics of different LN types imply important consequences for their computational properties and the olfactory processing that they perform. Type I LNs expressed differential branching patterns in different glomeruli suggesting a polar organization with defined input and output regions. According to this hypothesis, the synaptic input from a defined receptive field (e.g., one or a few glomeruli) would be integrated into action potential firing that would spread to other innervated glomeruli, and provide a defined array of glomeruli with synaptic input. In this model, glomeruli could interact independently of their distance: not only nearest-neighbor glomeruli could interact, but also glomeruli that are distributed throughout the entire antennal lobe. In contrast, type II LNs have very similar branching patterns in all glomeruli, suggesting that they can receive synaptic input from all innervated glomeruli. However, during odor stimulation, synaptic input will be typically restricted to certain glomeruli, in which graded postsynaptic potentials will be generated. These potentials will spread only within the same glomerulus or to glomeruli that are electrotonically

close to the stimulated glomerulus. To test these hypotheses we combine whole-cell patch clamp recordings and calcium imaging of single local interneurons.

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Poster

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Support: NIH-NCRR RR014166

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Title: The biogenic amine tyramine and its receptor (AmTyr1) in olfactory neuropils in the honey bee (Apis mellifera) brain

Authors: ***B. OBAYOMI**, I. SINAKEVITCH, B. H. SMITH;
SOLS, Tempe, AZ

Abstract: Biogenic amines are neuroactive compounds that are involved in a large repertoire of invertebrate and vertebrate behaviors including olfactory processing, learning and memory. We used the honey bee as a model to study the functional role and anatomical distribution of tyramine and its receptor in the olfactory network participating in odor processing. The antennal lobe of the honey bee is the anatomical and functional analog of the vertebrate olfactory bulb. The antennal lobe consists of an aglomerular neuropil that is surrounded by 160 glomeruli, where each glomerulus participates in coding a subset of odors. In our previous studies we demonstrated that each glomerulus is divided into two major areas. The cortex receives olfactory receptor inputs from axons of olfactory receptor neurons (ORNs). It contains dendrites of Projection Neurons (PNs), axons of which connect the antennal lobe to higher order processing centers. The core receives axons from local neurons (LNs) that synapse onto PNs (Sinakevitch et al., 2013). Tyramine modulates this network potentially at several points, but their precise anatomical distribution in the network has not been analyzed in detail. The present study is therefore aimed at studying the distribution of tyramine in the antennal lobe and mushroom bodies by using antibodies against tyramine and its receptor with combination of the neurobiotin tracing of neurons that are important components of the network. We found that neurons that express tyramine have particular varicose-like fibers that invade the aglomerular neuropil. We

also found that there are significant differences in the distribution of biogenic amine within a glomerulus. Tyraminergic fibers from VUM neurons are mostly located in the cortex area of glomerulus. The AmTyr1 receptor is located in the ORN processes in the glomerulus cortex. PNs also exhibited AmTyr1 in its ending in the calyces of the mushroom bodies. The distribution of tyramine and its receptor in the antennal lobe suggests that it targets different components of the network in the cortex area of glomerulus (ORNs, PNs or LNs). Our study predicts a complex role of tyramine in odor processing in the insect antennal lobe. The data could be used to unravel the neuroanatomical mechanisms of reward learning in early sensory processing.

Disclosures: **B. Obayomi:** None. **I. Sinakevitch:** None. **B.H. Smith:** None.

Poster

786. Olfaction: Olfactory Bulb

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NDSEG

NSF GRFP DGE-1247271

Title: Integrate-and-fire and firing-rate models for insect olfaction

Authors: *P. B. PYZZA[1], G. KOVACIC[1], D. CAI[2,3];
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Abstract: The functionality of olfaction is known to be shared among a range of phyla from insects to mammals. The locust is an important animal model for studying olfaction. Experiments suggest that odors, detected through receptors on its antennas, are relayed to sensory neurons in the antennal lobe. There, they trigger a series of synchronous oscillations, followed by slow dynamical modulation of their firing rates, which slowly subside after the stimulus has been removed. I model this behavior by using a conductance-based, sparsely-coupled, Integrate-and-Fire neuronal network with fast (~2-5 ms) excitatory and both fast (~4-10 ms) and slow (~30-100 ms) inhibitory conductance responses, driven by Poisson trains of external spikes. The fast inhibitory conductance response, together with the excitation, creates the initial oscillations that are believed to be responsible for the initial detection and brief

identification of the presented odor. The slow component of the inhibitory conductance then damps the oscillations, without completely eliminating them, and aids in the creation of the slow firing rate patterns that follow yet later. The insect is conjectured to identify the odor more precisely from these slow patterns. I have further derived a coarse-grained, firing-rate model that described the overall responses of the excitatory and inhibitory neuronal populations. In the absence of the slow inhibition, the model generates fast network oscillations as seen experimentally and in my numerical simulations. They arise as an attracting limit cycle. In the full model, after the presentation of an odor, the slow inhibition rises slowly, allowing for a period such oscillations, which are then shut off by the high level of inhibition for an extended period of time, before a much slower oscillatory pattern reemerges. This pattern is the result of a balance among the three types of conductances and between the two disparate timescales. I analyze mathematically the bifurcations associated with these changes of the dynamics.

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Poster

786. Olfaction: Olfactory Bulb

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Topic: D.01. Chemical Senses

Title: Computational mechanisms in the peripheral nervous system of the predatory sea-slug Pleurobranchaea

Authors: A. DUMAN[1], A. X. TRAN[1], B. B. M. SCHAUB[3], M. P. FLANAGAN[1], B. L. KLUSAS[3], D. I. VALLEJO[4], N. DELGADO[4], N. M. MADEIROS[4], E. BARRETO[4], S. R. MARTINEZ[4], M. W. MILLER[4], J. W. BROWN[2], *R. GILLETTE[3];
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Abstract: The peripheral nervous system (PNS) in the head regions of heterobranch (opisthobranch and pulmonate) molluscs performs computations functionally like those of vertebrate olfactory bulb and pallium. It encodes incentivizing qualities of chemotactile stimuli and their topographic locations, with sensory gain set by homeostatic need. The information is used by the CNS to compute motor decisions in approach-avoidance and feeding, and for learning values of potential prey and their defenses. The PNS in *Pleurobranchaea californica* shows profuse dopaminergic, GABAergic, and serotonergic immunoreactivity, suggesting the neurotransmitters' involvements in sensory computations. We tested effects of neurotransmitters

and pharmacological blockers on the chemotactile oral veil, observing behavioral responses to stimuli and spike discharge in sensory nerves. Topical unilateral application of the D2 blocker sulpiride to the oral veil increased latencies for approach turns to appetitive stimuli and decreased sensory nerve discharge, while appetitive responses were intact on the control side. GABA applied unilaterally caused avoidance responses to appetitive stimuli on that side, while the control side remained positively responsive. The GABA blocker bicuculline caused effects like GABA. But we found that defensive acid secretion (pH ~1.5) was induced by bicuculline but blocked by GABA. Acid secretion raises appetitive thresholds and induces avoidance. Thus, GABA and bicuculline exert similar effects through different pathways. Serotonin applied to the oral veil preparation enhanced sensory nerve discharge to appetitive stimuli. These observations suggest models in which inhibitory D2 receptors and GABA act within serial disinhibitory and recurrent inhibition pathways to provide initial computations of stimulus incentive and somatotopic mapping. Serotonin release in the PNS may regulate sensory pathway gain. As PNS serotonin originates in central neurons of the feeding network, release would be a function of both feeding network activity and hunger state.

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Poster

787. Sound Localization and Binaural Interactions

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NIDCD Grant DC03829

Title: Proteomic analysis of chick Nucleus Laminaris reveals potential FMRP substrates

Authors: *H. SAKANO[1], Y. WANG[2], W. S. NOBLE[1], M. J. MACCOSS[1], E. W. RUBEL[1]; [1]Univ. of Washington, Seattle, WA; [2]Florida State Univ., Tallahassee, FL

Abstract: The avian nucleus laminaris (NL) is an auditory nucleus in the brainstem that is structurally similar and functionally analogous to the mammalian medial superior olivary

nucleus (MSO) which is essential for low frequency for binaural processing. In addition, the chick NL is a useful model system for studying activity dependent dendritic plasticity, owing to the bipolar dendritic arbors that receive input from each ear and display rapid, profound and localized structural changes in response to a variety of afferent manipulations. These structural changes in dendrites are expected to involve immediate and local mechanisms such as signaling, protein modification and local translation. However, to date, the proteome of the nucleus laminaris is not known. Here we have identified 657 proteins that are expressed in the nucleus laminaris by using laser microcapture technique and tandem mass spectrometry. Gene ontology analysis reveals that many proteins are involved in mitochondria, translation, metabolism and cytoskeletal remodeling, suggestive of high metabolic demand and remodeling. Comparative analysis reveals 96 proteins that are putative substrates of FMRP (fragile X protein), which raises the possibility that these proteins are locally translated.

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Poster

787. Sound Localization and Binaural Interactions

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Research Fund KU Leuven OT/14/118

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Title: Binaural frequency tuning and timing in neurons from the chinchilla medial superior olive

Authors: ***M. SAYLES**, P. X. JORIS;
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Abstract: Sensitivity to micro-second inter-aural differences in timing of sounds is critical for azimuthal localization. It emerges in specialized neurons in the medial superior olive (MSO). MSO neurons are tuned to a particular inter-aural time difference (ITD); their “best delay” (BD). How neural circuitry creates ITD tuning is a matter of debate. Many hypotheses have been

proposed. Cochlear-tuning disparities leading to neural delays by virtue of cochlear travelling-wave delay ("stereausis") have received little experimental attention in mammals. Difficulties obtaining single-unit recordings from MSO neurons have hampered progress. Previously, our laboratory examined coincidence patterns between auditory-nerve-fiber spike trains from different cochlear locations. Very small inter-aural frequency-tuning disparities accounted for the range and positive (contra-leading) bias in BDs observed experimentally. However, the disparities need to be systematically biased, with ipsi-lateral inputs tuned to higher frequencies than contra-lateral inputs. Here we test the existence of such biased disparities. Using an approach modified from Bremen and Joris (2013), we recorded from ascending MSO axons in the lateral lemniscus (LL) as they project to the dorsal nucleus of the LL (DNLL) and the midbrain, in the anesthetized chinchilla. We presented inter-aurally correlated (+1) and anti-correlated (-1) 20-kHz bandwidth noise at a range of ITDs to construct noise-delay functions. Next, we presented inter-aurally uncorrelated (0) noise, and used spike-triggered reverse correlation to estimate the impulse responses of ipsi- and contra-lateral inputs independently. We cross correlated the impulse responses to predict the noise-delay function. Typically, firing rate as a function of ITD (noise-delay function) shows a damped oscillatory pattern. From the difference between +1 and -1 noise-delay functions, the "difcor", we determined the BD. Most, but not all, BDs were within the π limit, with a bias to positive ITDs. For most units the correlation between predicted and measured noise-delay functions was very good (>0.9). However, in a few units (thought to be DNLL cells receiving MSO inputs), this prediction was poor. We found significant inter-aural frequency-tuning differences (up to 1/3 octave) in many units. These were not systematically biased toward higher-frequency tuning ipsi-laterally. We conclude that frequency tuning (and therefore, timing) disparities exist and contribute to ITD tuning in the mammalian system. However, binaural cochlear disparities in themselves cannot account for the BD distribution observed.

Disclosures: **M. Sayles:** None. **P.X. Joris:** None.

Poster

787. Sound Localization and Binaural Interactions

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Title: Coincidence detection in the medial superior olive promotes responsivity to low-frequency narrowband sounds

Authors: *T. P. FRANKEN, P. X. JORIS;
KU Leuven, Leuven, Belgium

Abstract: The hearing and vocalization range of large-bodied land mammals, including humans, is geared towards low frequencies. Combined with large heads and widely separated ears, low-frequency hearing enables sound localization based on neural sensitivity to interaural timing differences (ITDs). In contrast, ultrasonic hearing is the rule in small mammals, where the brainstem circuits that process ITDs are minimal or even lacking. Curiously, some rodents are sensitive to low frequencies by virtue of dramatically enlarged middle ear spaces. These species are increasingly used as experimental models of human hearing and indeed have neurons sensitive to low-frequency ITDs. This is puzzling, since their small heads result in minuscule ITDs, which enable only coarse sound localization. We obtained *in vivo* whole-cell recordings in the medial superior olive (MSO) of the Mongolian gerbil under general anesthesia. We recorded sub- and suprathreshold responses to monaural and binaural tones over a range of frequencies, and to noise of differing bandwidths. We find that gerbil MSO neurons are surprisingly sensitive to bandwidth: they are much more responsive to low-frequency tones or narrowband noise than to wideband noise. The rate of subthreshold excitatory postsynaptic potentials (EPSPs) arriving at the neuron does not show the same sensitivity, in contrast to the correlation between EPSPs. Our findings show that the coincidence detection operation performed by MSO neurons boosts the response to low-frequency narrowband sounds. In combination with the presence of specialized bullas which increase sensitivity to low frequencies, this suggests that the MSO circuit has survival value in the detection of low-frequency sounds per se., i.e. a function which is not strictly binaural or spatial.

Disclosures: T.P. Franken: None. **P.X. Joris:** None.

Poster

787. Sound Localization and Binaural Interactions

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Title: Do non-dipole features of brainstem field potentials reveal inhibition in the medial superior olive?

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Abstract: Field potentials are a potentially rich source of data for monitoring neural activity *in vivo*. Ideally, one could infer cell-level dynamics from these population-level extracellular data, but solving this inverse problem is a challenge. In recent studies, we recorded and modeled the prominent, sound-evoked field potentials in the auditory brainstem of cats (the *auditory neurophonic*), of which neurons in the medial superior olive (MSO) are the primary generators (Mc Laughlin et al 2010, Goldwyn et al 2014). Here, we formulate a biophysically-constrained and semi-analytical method for relating these field potential data to MSO activity. We make two contributions: 1) Quantitatively accurate simulations of spatio-temporal patterns of neurophonic responses to pure tones with frequencies ranging from 500 Hz to 2000 Hz, and 2) Inference of waveforms that represent putative (population-averaged) synaptic drive to MSO neurons. In our previous studies, we described the dipole-like spatial profile of the neurophonic and interpreted these data in light of the distinctive physiology and morphology of MSO neurons. In the present work, we describe consistent, frequency-dependent departures from dipole patterns apparent in some recordings in responses to stimulation of the contralateral ear. We propose a parsimonious model to account for our observations: MSO neurons receive dendritic excitation and somatic inhibition and this combination of synaptic inputs – superposition of a dendritic-based dipole and a somatic-based, effective monopole – shapes the neurophonic. We model MSO neurons as a population of passive cables. Model neurons receive a mix of excitatory and inhibitory inputs and cable theory provides the bridge between synaptic inputs, cell-level membrane potential dynamics, and extracellular voltage. We use an optimization algorithm to identify the synaptic inputs that provide the best fit between simulated and *in vivo* field potentials. We propose that the "best fit" model inputs reflect *in vivo* excitation and inhibition and thus provide insight on the elusive connection between field potential recordings and cell-level dynamics. Inhibition in the model creates a monopole-like neurophonic response and has dynamics that are consistent with known *in vitro* properties of inhibition in the MSO. The putative (population-averaged) inhibition in the model is slow relative to excitation and precedes excitation in its cycle-by-cycle

timing. However, alternative interpretations of non-dipole features of the neurophonic are possible.

Disclosures: **J.H. Goldwyn:** None. **M. Mc Laughlin:** None. **E. Verschooten:** None. **P.X. Joris:** None. **J. Rinzel:** None.

Poster

787. Sound Localization and Binaural Interactions

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Topic: D.02. Auditory System

Support: NIH Grant R01 DC 011582

Title: Adeno-associated viral transfection and optogenetic manipulation of auditory brainstem regions

Authors: ***E. MCCULLAGH**[1], S. MINKOWICZ[2], A. KLUG[1];
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Abstract: Low-frequency sound localization relies upon the difference in the times at which sound reaches the two ears (interaural time difference; ITD). Depending on the location of the sound source along the azimuth, ITDs are very small for sounds originating from or near the midline, and increase up to several hundred microseconds for sounds originating directly from one of the two sides. Thus, ITDs systematically vary with location along the azimuth, and this cue is extracted and evaluated by the auditory system during the localization process. While the medial superior olive (MSO) is the nucleus performing the actual ITD analysis, both the medial and the lateral nucleus of the trapezoid body (MNTB and LNTB, respectively) project fast and well timed monaural glycinergic inhibition to MSO neurons. Several concepts have been put forward that explain how these inhibitory inputs contribute to ITD processing in mammals. Both the MSO but also the MNTB and LNTB are deep auditory brain stem nuclei, making them difficult targets for optogenetic manipulation. Additionally, the auditory brain stem is heavily myelinated, making it challenging to deliver light to neurons in these nuclei. We have successfully transfected MSO, MNTB and LNTB neurons with inhibitory light-sensitive adeno-associated viruses (both halorhodopsin and ArchT). Once the virus has been expressed in these brain areas, we have shown that we can reduce or eliminate sound-evoked multiunit neural activity with light. Until recently, experimental manipulations that allowed for fast and reversible

activation and inactivation of MSO, MNTB, and LNTB, thus preventing direct experimental tests of the function of this circuit were not possible. Successfully transfection and manipulation of this circuit will be able to lead us forward into further investigating the processing of sound and ITDs in the auditory brainstem.

Disclosures: E. McCullagh: None. **S. Minkowicz:** None. **A. Klug:** None.

Poster

787. Sound Localization and Binaural Interactions

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Topic: D.02. Auditory System

Support: NIH Grant R01 DC011582

Title: Anatomical and electrophysiological properties of neural inhibition change during development and along the tonotopic axis of the mouse MNTB

Authors: O. ALBRECHT[1], E. SALCEDO[2], *A. KLUG[3];
[1]Physiol. and Biophysics, [2]Cell and Developmental Biol., Univ. of Colorado Sch. of Med., Aurora, CO; [3]Physiol. & Biophysics, Univ. of Colorado, Aurora, CO

Abstract: Auditory information processing, especially sound localization processing, requires very temporally precise neural circuits. One of these well-timed circuits is the medial nucleus of the trapezoid body (MNTB), best known for its giant excitatory inputs from the contralateral antero-ventral cochlear nucleus (AVCN), the calyces of Held. One of the MNTB's most intriguing features is that principle neurons also receive substantial inhibitory glycinergic input. We have recently shown that at least the majority of this inhibition originates from the ipsilateral ventral nucleus of the trapezoid body (VNTB). Here, we examined the developmental changes of this inhibition in the mouse and more specifically, how these changes occur in three broader tonotopic areas of MNTB (lateral = low, central = medium and medial = high frequency areas), using both anatomical and electrophysiological methods. We used an automated MATLAB algorithm to count immunolabeled GABAergic, glycinergic and "mixed" (i.e. containing both GABA and glycine) synaptic boutons and measured their size in these tonotopic areas. In electrophysiological experiments, we recorded mini-IPSCs and stimulated inhibitory inputs electrically to test for differences in the (pre)synaptic makeup between medially, centrally and laterally located MNTB neurons. We also tested for differences in postsynaptic receptor density by puffing glycine and the specific GABAA agonist muscimol onto MNTB principal neurons.

We found that shortly after hearing onset (p 14-16), profound anatomical and electrophysiological changes take place in the different frequency areas of the MNTB, which result in the establishment of a tonotopic "gradient" of inhibition that is also present in the adult animal (p 40+). For example, glycinergic boutons are larger in the most medial and the most lateral parts of the MNTB, suggesting a stronger inhibitory input for high- and low-frequency neurons. Another interesting finding is that the lateral portion of the MNTB seems to receive relatively less synaptic inputs of the "mixed" type than the central (= medium frequency) and the medial (= high frequency) areas. Finally, in terms of synaptic strength, the lateral (= low frequency) neurons show the largest IPSC amplitudes, whereas central MNTB neurons exhibit the smallest electrically elicited IPSC peaks, consistent with the anatomical results. This differential setup of inhibition along the tonotopic axis of the MNTB is suggestive of an important role this inhibition might be playing in auditory processing.

Disclosures: **O. Albrecht:** None. **E. Salcedo:** None. **A. Klug:** None.

Poster

787. Sound Localization and Binaural Interactions

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Amelia-Peabody Scholarship from MEEI

Title: Rate and temporal coding of dynamic ITD and amplitude modulation in the inferior colliculus may explain differences in psychophysical detection limits

Authors: ***N. ZUK**[1,2,4], B. DELGUTTE[1,3,2,4];
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Abstract: Humans cannot detect temporal variations in binaural cues such as interaural correlation or interaural time differences (ITD) at frequencies above 20-50 Hz where they can

still detect monaural amplitude modulation, suggesting that binaural processing is "sluggish" compared to monaural processing (Grantham & Wightman, J. Acoust. Soc. Am. 63:511; Grantham, J. Acoust. Soc. Am. 72:1178). Even so, broadband noise with a time-varying ITD remains discriminable from spatially-static noise at frequencies above 50 Hz (well above typical frequencies of natural motion), and this ability cannot be entirely explained by detection of monaural cues. In the inferior colliculus of the auditory midbrain, many neurons exhibit tuning to the frequency of both time-varying ITD and amplitude modulation in both their average firing rate and phase-locking strength. It is possible that similar biomechanisms (synaptic or channel-based) are responsible for producing such tuning. Very few studies, however, have compared tuning to time-varying ITD and time-varying amplitude in the same neurons. Here, we compared the neural coding of dynamic ITDs and diotically-presented sinusoidal amplitude modulation (SAM) by the same single units in the IC of unanesthetized rabbits. Our goal was to assess if dynamic binaural and monaural cues produce similar tuning in the IC and evaluate whether differences in tuning could account for differences in psychophysical detection. Tuning across modulation frequency was distinct for broadband noise with dynamic ITD compared to SAM with respect to both firing rate and phase-locking strength. Both the frequency of maximum phase-locking and the upper frequency limit of phase-locking were lower on average for dynamic ITD than for SAM. This finding may be a neural correlate of binaural sluggishness. While tuning of average firing rate to dynamic ITD was weak relative to SAM, median firing rates across our neuronal sample for modulation frequencies above 64 Hz deviated significantly from the average firing rate to an unmodulated stimulus presented at the center of the range of dynamic ITDs. This effect may explain the detectability of time-varying ITDs at high frequencies observed psychophysically. Overall, our results suggest that the mechanisms underlying sensitivity to time-varying binaural and monaural features are at least partly distinct and that these differences may explain the differences in psychophysical detection limits observed in humans.

Disclosures: **N. Zuk:** None. **B. Delgutte:** None.

Poster

787. Sound Localization and Binaural Interactions

Location: Hall A

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Topic: D.02. Auditory System

Support: RO1 DC007690

Title: Emergence of hemispheric spatial tuning in the owl's auditory forebrain

Authors: *M. V. BECKERT, J. L. PENA;
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Abstract: Previous work has shown that the auditory forebrain structure, Field L, which is homologous to mammalian primary auditory cortex (A1), and one of its downstream nuclei that is important for sound localization, the auditory archistriatum (AAr), which is homologous to the auditory portion of the mammalian frontal eye fields (FEF), lack a topographic representation of auditory space and are organized into clusters of similarly tuned neurons. This contrasts with the topographic distribution of spatial tuning observed in the avian superior colliculus. A similar difference is observed between the superior colliculus and auditory forebrain in mammals. Unlike in the midbrain, how auditory space in encoded in the forebrain is largely unknown. We are investigating this question in the auditory forebrain of the barn owl, Tyto alba. In particular, we are studying the transition from midbrain to Field L and from Field L to AAr. We improved upon previously used techniques by utilizing tetrode recordings to directly address the existence of these clusters and gather further insight into the organization of local populations in avian cortex. Tetrode recordings were performed in anesthetized barn owls. Sound stimuli were presented dichotically through custom made earphones, varying interaural time (ITD) and level difference (ILD), or from free-field speakers to obtain tuning profile of multiple single units within a single recording site. Tuning profiles of units within these local populations were then compared to one another to assess the similarity or difference in their composition. Our results in Field L are inconsistent with the clusters hypothesis and suggest a heterogeneous organization of neuronal tunings similar to mammalian A1. Groups of neighboring neurons can be tuned to very different combinations of binaural cues. In contrast, neighboring neurons in AAr, as well as neurons from different recording sites, have very similar tunings, suggesting that AAr is far more homogeneous than Field L. Additionally, AAr neurons show a stereotypic spatial tuning and a population response consistent with the emergence of a hemispheric population responding broadly to contralateral space, as proposed for mammals.

Disclosures: M.V. Beckert: None. **J.L. Pena:** None.

Poster

787. Sound Localization and Binaural Interactions

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Topic: D.02. Auditory System

Support: DFG grant WA 606/20-2

Title: Spectro-temporal integration in sound localization as revealed by frequency-modulated tones in barn owls

Authors: *L. KETTLER, H. WAGNER;
Inst. of Biol. 2, RWTH Aachen Univ., Aachen, Germany

Abstract: We used frequency-modulated sounds to study temporal integration in sound localization in the barn owl. Two barn owls were trained to respond to a sound in which the location was specified by the interaural time difference with a head turn towards the perceived sound direction. In such a situation, barn owls turn their head towards the perceived sound source, if broadband noise is used as stimulus. If the stimulus is narrowband, so-called phantom-source localizations may occur, indicating that the barn owl perceives two images. We hypothesized that frequency-modulated sounds might lead to similar behavior as stationary sounds, if a temporal window is taken into account. We further hypothesized that the size of the temporal window may be estimated from the percentage of phantom-source localizations when the bandwidth and duration of the frequency-modulated sounds were varied. We show that indeed the phantom-source localizations mainly depend on the bandwidth but to lesser extent on the duration of the frequency-modulated sounds. The time windows derived by using a running cross-correlation model with across-frequency integration and by comparing the responses to stationary and frequency-modulated sounds varied between 2ms and 17 ms, depending on the individual owl. Thus, the binaural process underlying frequency integration is not (moderately) sluggish when frequency-modulated sounds are used as stimuli.

Disclosures: L. Kettler: None. **H. Wagner:** None.

Poster

787. Sound Localization and Binaural Interactions

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Topic: D.02. Auditory System

Support: NIH Grant T32 DC000023

NIH Grant R01 DC03180

Title: Binaural contributions and cellular mechanisms underlying sound location sensitivity in the awake marmoset auditory cortex

Authors: *Y. WANG, X. WANG;
Biomed. Engin., Johns Hopkins Univ., Baltimore, MD

Abstract: Sound localization is a crucial ability for survival, as both animals and humans can rapidly detect stimuli originating from any direction within the environment. To understand how spatial location is processed by individual auditory cortex neurons, we performed extracellular and intracellular recording experiments in awake marmosets, a highly vocal arboreal New World primate, using both free-field and dichotic stimuli. First, using extracellular recording and sounds presented through dichotic earphones, we tested to what degree the primary auditory cortex (A1) processes azimuth information. We found that most A1 neurons responded to monaural stimuli to either ear. The response to sound from the contralateral ear was overall stronger across the population. Binaural interactions were observed in the majority of neurons recorded. We found that rate-level functions can have different characteristics for the two ears, for example, being monotonic in one and non-monotonic in the other. Overall, tuning to the interaural level difference (ILD) measured dichotically was well correlated with spatial sensitivity mapped using 32 free-field speakers placed all around the animal, including spaces above, below and behind the animal. Level-dependent changes in spatial sensitivity in free-field corresponded to changes in sharpness of ILD functions at different sound intensities. The intracellular recording showed that the subthreshold inputs to A1 neurons are broadly tuned in space. This is in contrast to the spiking response recorded from the same neuron, which is more narrowly tuned to space, indicating that spatial sensitivity is actively refined at the level of single A1 neurons. Many neurons showed level-invariance and sometimes contraction with increased sound intensity. For neurons that showed expansion in spatial sensitivity at louder sound levels, the enlarged spatial receptive fields approached the extent of spatial sensitivity in the subthreshold response. The intracellular recordings also indicated that inhibition plays a role in shaping spatial receptive field. Our observations suggest that azimuth tuning in A1 arises at least partially at the cortical level through binaural interactions and further refined from its thalamic inputs.

Disclosures: **Y. Wang:** None. **X. Wang:** None.

Poster

787. Sound Localization and Binaural Interactions

Location: Hall A

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Topic: D.02. Auditory System

Support: NIH R01-DC011548

Title: Temporal weighting of binaural cues in human auditory cortex: an fMRI study

Authors: *N. C. HIGGINS[1], S. A. MCLAUGHLIN[3], G. STECKER[2];
[1]Hearing and Speech Sci., [2]Vanderbilt Univ., Nashville, TN; [3]Univ. of Washington, Seattle, WA

Abstract: When human listeners localize sounds in space, their judgments reflect weighted combinations of the available acoustic cues. For horizontal localization, the primary cues are the interaural time (ITD) and level differences (ILD). In real world listening, these cues fluctuate over time, yet perception remains stable. That stability reflects the perceptual dominance of cues occurring at particular times in the duration of a sound: the ITD at sound onset and the ILD at onset and offset. For both cues, the middle part of the sound appears remarkably ineffective, suggesting a dissociation between perception and the physical features of the stimulus. In order to determine whether spatial processing in the human auditory cortex (hAC) reflects the perceived versus physical features of sounds, functional magnetic resonance imaging (fMRI) was used to measure activity in response to 1 s trials which varied in ITD or ILD (nine values spanning left to right) in separate runs. Each trial presented trains of 16 narrowband clicks in which the binaural cue was applied equally to all clicks (referred to as "full-cue") or only to the first click ("onset"), in which case clicks 2-16 carried zero ITD and ILD. Listeners performed a simple pitch-change detection task to ensure vigilance. Image acquisition employed a continuous event-related design (TR=2s, 3 Tesla, 2.75 x 2.75 x 3mm resolution). Data were analyzed using general linear modeling and parcellated into regions of interest corresponding to hAC using Freesurfer. Cortical responses to full-cue ILD stimuli in each hemisphere were larger for contralateral than ipsilateral ILDs, and exhibited a minimum around ILD=0. Onset ILD stimuli also elicited large responses to contralateral ILDs, but additional elevated responses near 0 dB ILD (i.e., when onset and post-onset ILDs matched) and conspicuous response minima at intermediate ILDs of +10 dB were also observed. Unlike ILD stimuli, but consistent with previous fMRI studies of ITD processing, the ITD response functions were relatively flat in both conditions, and displayed little contralateral dominance despite strong overall activation to sound. These results were used to evaluate competing models of AC population response, including topographic, opponent-channel, and three-channel models incorporating mechanisms of response adaptation, forward suppression, and lateral inhibition. Overall, the pattern of results for full-cue and onset ILD parallels the psychophysical results that perception is influenced by both stimulus onset and offset ILD cues, and provides evidence that hAC maintains sensitivity to ILD of the onset and later portions of the sound.

Disclosures: **N.C. Higgins:** None. **S.A. McLaughlin:** None. **G. Stecker:** None.

Poster

787. Sound Localization and Binaural Interactions

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Netherlands Organization for Scientific Research (NWO), Middlegroot Grant 480-09-006

Title: The representation of sound azimuth in the auditory cortex of early blind humans

Authors: *K. DEREY[1], E. FORMISANO[1], G. VALENTE[1], M. ZHAN[1], R. KUPERS[2], B. DE GELDER[1];
[1]Cognitive Neurosci., Maastricht Univ., Maastricht, Netherlands; [2]Inst. for Neurosci. and Pharmacol., Univ. of Copenhagen, Copenhagen, Denmark

Abstract: Early visual deprivation often leads to the development of superior sound localization abilities compared to sighted individuals3,5. The development of these enhanced spatial hearing skills can be explained by functional recruitment of the deprived visual system or by neural plasticity of the intact auditory modality, or by a combination of both. The present fMRI study investigates functional plasticity of the representation of acoustic azimuth in human auditory cortex following early visual deprivation. Methods Stimuli: Stimuli were recorded with binaural microphones in the ear canal of each participant whilst sounds were presented with a 3D sound system. This set-up maximizes the availability of spatial cues in each recording. Sounds consisted of a low (250-700Hz) or higher (600-1.400Hz) frequency modulated tone rotating smoothly in the horizontal plane around the head (full circle in 40s). Scanning: We scanned 8 EB subjects with a 3T MRI scanner. Recordings of the stimuli were presented binaurally at three intensity levels (10dB difference in between) in a passive design. Functional runs were collected using a standard EPI sequence (TR: 2000ms, 32 slices, 2mm iso-voxels). An anatomical image was obtained with a T1-weighted scan. Data of 8 sighted controls (SC) was acquired during a prior experiment with an equivalent design 2. Analysis: Functional data were preprocessed with correction for motion, slice scan time and low frequency drifts (BrainVoyager QX). We constructed a response azimuth function (RAF) per trial for each auditory responsive voxel (GLM, auditory > baseline) using a Finite Impulse Response (FIR) deconvolution. We estimated from the RAF the best azimuth position as well as the steepest slopes. Additionally, a GLM was estimated with binaural sum and difference predictors to identify spatially sensitive voxels. Results Presentation of sounds activates the auditory cortex (AC) both in EB (data of two subjects) and in SC (FDR, $q < 0.05$). RAFs indicate that azimuth tuning may be more homogeneously distributed across the azimuth in EB than in SC. Tuning width distributions of both EB and SC show 2 distinct populations, one with narrow and one with broad tuning. Finally, spatially sensitive regions appear to be located in AC as well as in occipital and parietal

regions in EB. These areas are concentrated in the AC in SC. Conclusion Our data suggests that there are both similarities (e.g. tuning width) and differences (e.g. location preference) between the cortical representation of acoustic azimuth in sighted and early-blind individuals. These differences may contribute to the enhanced auditory localization abilities observed in early blind humans.

Disclosures: K. Derey: None. **E. Formisano:** None. **G. Valente:** None. **M. Zhan:** None. **R. Kupers:** None. **B. de Gelder:** None.

Poster

787. Sound Localization and Binaural Interactions

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 787.13/L34

Topic: D.02. Auditory System

Title: Improving binaural sensitivity in noise using a novel speech-processing algorithm

Authors: *Y. GAI, ESQ, L. M. KUJAN, J. G. CIANCIBELLO;
Biomed. Engin., St. Louis Univ., Clayton, MO

Abstract: When the environment is quiet, cochlear implants provide hearing-impaired patients with adequate speech intelligibility. However, due to those patients' degraded ability to spatially separate sound sources, speech perception quickly degrades as background noise increases. Recent psychophysical and physiological studies using sharpened envelopes have pointed toward a possible solution to the problem. Although promising, this strategy has only been tested with simple tone/noise sounds. Here we proposed a novel speech-processing algorithm that applies the concept of envelopes enhancement to any input sound, including speech. The algorithm was examined in normal-hearing listeners through headphone with noise-vocoded speech to simulate implant hearing. The measured thresholds of interaural time differences (ITDs) contained in speech envelope in quiet were on the order of a few hundred microseconds, and our algorithm significantly improved the thresholds compared with standard algorithms of cochlear implants. Speech-perception tests confirmed that the envelope sharpening did not degrade intelligibility. An unexpected finding was that, when binaurally-coherent noise was introduced, the envelope-ITD thresholds improved dramatically (from hundreds to tens of microseconds), almost as good as the thresholds of carrier-ITDs. Our finding suggest that bilateral cochlear implants may benefit from the presence of an artificial timing signal presented synchronously across the two ears.

Disclosures: **Y. Gai:** None. **L.M. Kujan:** None. **J.G. Ciancibello:** None.

Poster

787. Sound Localization and Binaural Interactions

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 787.14/L35

Topic: D.02. Auditory System

Support: St. Olaf College

Title: A comparison of free-field and headphone based sound localization using SoLoArc: A modular and portable, audiovisual, free-field localization device with high spatial resolution

Authors: ***J. A. WESTERBERG**[1], A. R. BALHORN[1], R. S. TYSHYNSKY[1], J. L. LOEBACH[2];
[2]Psychology, [1]St. Olaf Col., Northfield, MN

Abstract: Sound localization is often demonstrated using artificial ITD and ILD cues presented over headphones. Such tasks can be confusing, difficult for undergraduates to administer and interpret, and prone to experimental errors compared to free-field localization. Over the past 8 months we have designed and fabricated a portable audiovisual localization device. Here, we describe the construction of the SoLoArc, and present data from 3 studies, demonstrating that the device works as intended, and produces more accurate localization in the free-field azimuth compared to ILD and ITD cues presented over headphones. The device presents auditory stimuli in a 180° arc from speakers placed every 5° on the concave surface. A participant is seated at the point of convergence of the sound field, 4 feet from each speaker. An array of 73 LEDs allows the investigation of visual influence in localization tasks. The arc can be positioned for azimuth, front/back, or vertical localization. The participant's head may be fixed or freely moving. The device is interfaced to a PC using 2, 96-channel NI USB I/O devices. Matlab is used for device control allowing stimuli of any frequency and intensity to be created and delivered from each speaker independently. Preliminary tests of the device demonstrate its validity and utility. 48 undergraduates enrolled in a Sensation & Perception course completed 3 sound localization activities. Participants completed a headphone based task using ITDs as the primary cue. 440 Hz sinusoids were presented from the left and right headphones with delays ranging from 640 μsec (right ear lead) to -640 μsec (left ear lead). Sound locations were chosen from one of 4 randomized lists and participants responded by indicating an angle from where they thought the sound source emanated using a worksheet. Participants completed the same task using ILDs as the primary cue. 6000 Hz sinusoids were presented from the right and left headphones with

intensity differences ranging from +/- 21 dB between right and left ear locations. Finally, participants completed a free-field localization task using SoLoArc. Participants were presented with speaker locations from one of 8 randomized lists composed of 1000 Hz sinusoids at 70 dB, and indicated their response by pointing a laser at a metric attached to the face of the device, which was recorded by an experimenter. Regression analyses revealed that while each method was related to the ideal, β coefficients were higher for the free-field condition (β=.995) than the ILD (β=.905) or ITD conditions (β=.949). In addition to increased accuracy, participants reported that the free-field task was easier to complete and more natural and intuitive.

Disclosures: J.A. Westerberg: None. **A.R. Balhorn:** None. **R.S. Tyshynsky:** None. **J.L. Loebach:** None.

Poster

788. Cross-Modal Processing: Neural Circuitry and Development

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Program#/Poster#: 788.01/L36

Topic: D.03. Multisensory Systems

Support: FAPESP nº 2008/02771-6

Title: GABAergic projections from the ventral cochlear anterior nucleus to the cochlear root neurons

Authors: *N. O. BARIONI[1], M. G. MARTINS[2], A. V. DA SILVA[3], R. G. NIETO[4], M. E. LÓPEZ GARCIA[4], J. C. HORTA JÚNIOR[2];
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Abstract: The cochlear root neurons (CRN) are the first in the central nervous system to receive the acoustic information. They are in connection with sensory integration centers in the brainstem, particularly the pontine caudal nucleus. The CRN are related to the the acoustic startle reflex (ASR) fundamental neural circuit. The ASR shows various modulations which are important in clinical diagnostics of psychiatric and neurodegenerative illnesses. Startle modulations are promoted by influences from several nuclei on its fundamental neural circuit. The cochlear root nucleus is the least studied nucleus of this circuit. It's afferents' origins and neurochemical identity remain unclear. Recently it was described lots of GABAergic buttons making connection with the CRN soma and dendrits, which would propose an inhibitory

modulation upon these neurons, however the source of this projections is still unknown. One possible source could be the ventral cochlear anterior nucleus (VCA), which is mainly GABAergic and indirectly projects to the CRN through a pathway composed by the inferior colliculus and ventral nucleus of trapezoid body. . Knowing VCA's GABAergic neurochemistry and due to the proximity of this nucleus to the CRN and to confirm previous tract-tracing studies that indicate afferent connection from VCA to CRN, we investigated a direct GABAergic projection from VCA to the CRN. To achieve this purpose, stereotaxic surgery with an injection of BDA (anterograde neurotracer) was performed in 3 adult Wistar rats (100 days). After 7 days, animals were perfused, the brains were collected and processed combining imunohistochemistry protocols for BDA, GABA and VGluT1. Results showed BDA labeled axon terminals in apposition with CRN soma and dendrits. Besides, confocal analisys showed a colocalization between imunolabelled GABAergic and BDA fibers and terminals. This GABAergic projection suggests an inhibitory role directly upon the CRN, probably being related to ASR modulations.

Disclosures: **N.O. Barioni:** None. **M.G. Martins:** None. **A.V. Da Silva:** None. **R.G. Nieto:** None. **M.E. López Garcia:** None. **J.C. Horta Júnior:** None.

Poster

788. Cross-Modal Processing: Neural Circuitry and Development

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Topic: D.03. Multisensory Systems

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CNPq

CAPES

Title: Cortical circuits involved in skilled forelimb movements and tool use

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Abstract: Cebus monkeys stand out from other New World monkeys by their ability to perform fine hand movements and use tools. The posterior parietal cortex (PPC) plays a crucial role in the implementation of such behaviors working as a cortical node for visual, somatosensory and

motor integration. However, the neural substrate underpinning this function was still not fully elucidated. In the present study we described the corticocortical connectivity of different sectors of areas 5 and 7 of the PPC in the cebus monkey. After a brief electrophysiological mapping, five adult cebus monkeys were injected with fluorescent tracers at (a) hand/forearm representation of area 5 (area 5v), (b) posterior bank/border of the intraparietal sulcus (IPS), corresponding to the expected location of the anterior intraparietal area (AIP) and area PFG, and (c) area PF. After a survival of 11-14 days, animals were perfused. Retrogradely labeled neurons were plotted using a fluorescent microscope equipped with the Neurolucida system (MBF, Inc). Architectonic identification of cortical areas was performed on adjacent Nissl-stained, myelin-stained, or SMI-32 immunoreacted sections. The representation of hand/forearm in area 5v received many projections from somatosensory areas 3a, 3b, 1, 2, and S2/PV. In the PPC, labeled cells were found mainly in the anterior bank of the IPS (5d and MIP) and in area PF. In the frontal cortex, dense connectivity was observed with motor (F1) and premotor areas (F2, F4 and F5). In contrast, injections in the posterior bank/border of the IPS (in area AIP/PFG) revealed dense projections from the inferior parietal cortex (PG, PFG and PF), from area PO, and from areas of the posterior bank and caudal portion of IPS. Many labeled cells were also observed in F1 and premotor areas (mainly area F5). Area AIP/PFG was also connected with prefrontal fields, SII/PV, face representation of area 2, and higher order visual areas of the inferior temporal lobe. After injections in area PF, labeled cells were found in the anterior (face representation of area 2), posterior (5v, MIP, VIP, PFG and PG), and lateral parietal cortex (S2/PV). In the frontal lobe, area PF was densely connected with F1, F4,F5 and prefrontal fields. These results suggest that the cortical circuits involved in the somatosensory-motor integration for manual behaviors (area 5v) are segregated from the cortical circuits that are implementing the visuomotor integration (area AIP/PFG). Area 5v presents none or very weak connectivity with area AIP/PFG, while area PF is densely connected with both areas. Therefore, area PF could be playing a crucial role in the functional integration of somatomotor and visuomotor circuits.

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Poster

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Wallace Foundation

Title: Immature corticotectal influences initiate the development of multisensory integration in the midbrain

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Abstract: Neonatal neurons in the cat superior colliculus (SC) develop the capability to integrate cues across sensory modalities (e.g., visual-auditory) in early postnatal life. The developmental chronology of this highly complex process is puzzling because it is axiomatic that development of cortex is delayed relative to that of the midbrain, yet development of this midbrain integrative process is known to be dependent on inputs from cortex (i.e., especially the anterior ectosylvian sulcus, AES). One possibility is that the axiom is too broad and, in this case, the corticotectal neurons in AES that are critical for this midbrain process (i.e., unisensory AES neurons) reach functional maturity sooner than expected. To examine this question, single neurons were simultaneously recorded from the SC and AES in groups of animals at different ages (4-22 weeks). The results showed that the development of SC multisensory integration begins at the time at which correlated AES-SC activity is first seen. This functional corticotectal connectivity appears to be the key to initiating the development of this midbrain process. Unexpectedly, however, a surprisingly low level of AES unisensory maturity appears to be required. Even when SC multisensory integration is effectively adult-like, the visual and auditory latencies of AES neurons are nearly twice what they will ultimately be, their responsiveness remains prolonged, response thresholds continue to be high, and their receptive fields are not yet mature. Thus, SC multisensory integration can reach an adult-like state of maturity even while relying on immature, yet functional, corticotectal inputs. Supported by NIH grants EY016716, EY022458, T32NS073553, and a grant from the Wallace Foundation.

Disclosures: R.L. Miller: None. **B.A. Rowland:** None. **B.E. Stein:** None.

Poster

788. Cross-Modal Processing: Neural Circuitry and Development

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Support: NIH Grant NS054731

Title: Modulation of vertebrate sensorimotor neural circuits by the neuropeptide, arginine vasotocin

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Abstract: Arginine vasotocin (*avt*) and its mammalian homolog, arginine vasopressin (*avp*), are linked to many complex behaviors including aggression and reproductive behaviors presumably by modulating neural circuits. However, how AVT/AVP regulates neural circuits is unclear. In zebrafish embryos, *avt* is expressed by neurons in the preoptic area of the diencephalon and vasotocin receptors (*avtrs*) by numerous neurons in the CNS during embryogenesis prior to any social behavior. Some of the *avtr*+ neurons in the posterior hindbrain appear to receive sensory input and likely project axons into the spinal cord at a time when embryos respond to tactile and chemical stimulation with motor responses such as swimming. *avtr* is also expressed in the mechanosensory neurons in the dorsal spinal cord. Based upon these findings we hypothesized that signaling by AVT may modulate sensorimotor circuits and thus motor responses to sensory stimulation. This hypothesis predicts that *avtr*+ neurons respond to sensory stimulation, and that increasing and decreasing AVT signaling, respectively, enhance and inhibit touch-induced swimming. The activities of neurons in the hindbrain were examined by cFos transcription as a proxy for neural activation. Neurons found in the same region of the hindbrain as the *avtr*+ neurons were found to increase cFos transcription in response to sensory stimulation of the embryo consistent with *avtr*+ neurons being responsive to sensory stimulation. Perturbation of AVT signaling by pharmacological and molecular manipulations resulted in predicted changes in mechanosensory and chemosensory induced swimming in embryos. Furthermore, photoreceptors are expressed by neurons in the preoptic region which also expresses *avt* suggesting the possibility that light may modulate the release of AVT. In fact we found that responses to tactile stimulation were enhanced in the light compared with the dark and that light enhancement required AVT signaling. These experiments suggest that AVP/AVT signaling modulates sensorimotor circuits and responses and further suggests that AVP/AVT signaling may serve a similar modulatory function in neural circuits regulating social and reproductive behaviors.

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Poster

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Program#/Poster#: 788.05/L40

Topic: D.03. Multisensory Systems

Title: Smell's melody: Brain network involved in multisensory interactions between sounds and odors

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Abstract: Multisensory interactions are constantly present in our everyday life and allow a unified representation of environment. Cross modal integration is often studied in multisensory associative brain regions, but recent findings suggest that most of the brain could be multisensory (A. Ghazanfar and C. Schroeder, Trends in Cognitive Sciences, 2006). Indeed, recent studies have shown that integration could also occur in primary sensory cortices, previously considered to be unimodal. This finding has modernized our view of brain organization and open new perspectives for the multisensory research field. At this time, we still don't know how the brain deals with information from different sensory systems. In this project, we want to understand whether the establishment of neuronal oscillations can functionally connect sensory regions and take part of the multisensory integration, and how this connection is built up by learning. For this, we examine changes in the cortical network involved in the acquisition of a multisensory association between a sound and an odor in rats, through the analysis of the local field potentials' oscillations. The originality of the project is to sample a large network of brain structures including primary sensory cortex (primary auditory cortex, olfactory bulb) and multimodal areas towards which converge these two senses: the piriform and perirhinal cortices. We have developed a behavioral GO/NO GO test in which the rat must combine simultaneous auditory and olfactory informations to succeed. Data and brain signals obtained in this task suggest that the power of oscillations in different frequency bands within the targeted areas and the coherence of oscillations between these areas are modified by the multisensory learning.

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Poster

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Topic: D.03. Multisensory Systems

Support: DFG SFB TRR 31

Title: Anatomical pathways for short-latency multisensory integration processes in primary sensory cortices A1, S1, and V1

Authors: J. U. HENSCHKE[1], T. NOESSELT[4], H. SCHEICH[2], *E. BUDINGER[3];
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Abstract: Multisensory integration does not only recruit higher-level association cortex, but also low-level and even primary sensory cortices. Here, we will describe and quantify two types of anatomical pathways, a thalamocortical and a corticocortical that possibly underlie short-latency multisensory integration processes in the primary auditory (A1), somatosensory (S1), and visual cortex (V1). Results were obtained from Mongolian gerbils, a common model-species in neuroscience, using simultaneous injections of different retrograde tracers into A1, S1, and V1. Several auditory, visual, and somatosensory thalamic nuclei project not only to the primary sensory area of their own (matched) but also to areas of other (non-matched) modalities. The crossmodal output ratios of these nuclei, belonging to both core and noncore sensory pathways, vary between 0.4 and 63.5 % of the labeled neurons. Approximately 0.3 % of the sensory thalamic input to A1, 5.0 % to S1, and 2.1 % to V1 arise from non-matched nuclei. V1 has most crossmodal corticocortical connections, projecting strongest to S1 and receiving a similar amount of moderate inputs from A1 and S1. S1 is mainly interconnected with V1. A1 has slightly more projections to V1 than S1, but gets just faint inputs from there. Concerning the layer-specific distribution of the retrogradely labeled somata in cortex, V1 provides the most pronounced feedforward-type outputs and receives (together with S1) most pronounced feedback-type inputs. In contrast, A1 has most pronounced feedback type outputs and feedforwardtype inputs in this network. Functionally, the different sets of thalamocortical and corticocortical connections could underlie distinctive types of integration mechanisms for different modality pairings.

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Poster

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Tab Williams Foundation

Title: Underestimating superadditivity in multisensory integration

Authors: *B. A. ROWLAND, A. S. DAKOS, T. R. STANFORD, B. E. STEIN;
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Abstract: Multisensory neurons in the superior colliculus (SC) integrate concordant signals derived from different sensory modalities to produce enhanced responses. The quantitative framework traditionally used for reckoning the products of such multisensory integration is based on changes in the average number of impulses elicited from a neuron on a given trial. According to this simple quantification, superadditive computations (i.e., a multisensory response greater than the sum of the component unisensory responses) are only found in a minority of samples, most frequently those in which the sum of the averaged unisensory responses is less than 5 impulses. Based on summing activity over a protracted stimulus epoch, this “rule of thumb” implies that superadditive computations are represented only on the lower tail of a distribution of multisensory products, and found only when neurons are responding near their threshold. The present study questions the veracity of this inference. Two important factors must be considered in this context: 1) the moment-by-moment computations yielding the integrated multisensory products change during a neuron’s response window, and 2) interspersed with neurons that are overtly responsive to each sensory input (the typical multisensory neuron used in most studies) are many "covert" neurons which exhibit multisensory integration, but do not respond overtly to one of the component sensory inputs. To examine the impact of these two factors on multisensory integration, we evaluated the moment-by-moment products of integrating visual and auditory signals in both single neurons and multi-neuron recordings in the SC of both awake and anesthetized animals. The data show that superadditive enhancement is an exceedingly common computation in the early response window of both preparations (~100ms after stimulus onset), a period that includes the response onsets and peaks for both sensory inputs. It is rare for it not to be present. This early enhanced multisensory response proved not only to be more potent, but to be statistically more reliable. Furthermore, due to the presence of covert neurons, results from most single neuron analyses significantly underestimate the potency of multisensory enhancement within the local circuit, and do so by a multiplicative factor. Thus the emergent picture of SC multisensory integration is one in which a dynamic process produces

a wave of enhancement to the downstream neuron that is dominated by a leading edge of superadditivity.

Disclosures: **B.A. Rowland:** None. **A.S. Dakos:** None. **T.R. Stanford:** None. **B.E. Stein:** None.

Poster

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Support: NIH Grant DC0007156

Title: Audiovisual integration in primate dorsolateral prefrontal cortex

Authors: ***A. POREMBA**, J. BIGELOW;
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Abstract: Audiovisual integration underlies a wide range of adaptive behaviors in humans and other primates, including language and communication, recognizing individual conspecifics, and social decision-making. Neurobiological studies spanning the last several decades suggest audiovisual integration is enabled by convergence of auditory and visual inputs upon individual neurons at multiple sensory processing stages, and includes interactions among numerous cortical and subcortical brain regions. Among these regions is the lateral prefrontal cortex (PFC), which may be particularly important for selecting appropriate actions in response to audiovisual cues. Neurophysiological studies have concentrated on audiovisual integrative functions within the ventrolateral division of PFC (Romanski, 2012), largely because of its purported role in the ventral object-processing stream. Comparatively little is known about audiovisual integration within dorsolateral PFC, which is believed to form part of the dorsal spatial-processing stream. Motivated by neuroimaging data suggesting auditory-visual overlap in dorsolateral PFC, as well as anatomical findings revealing connections between ventrolateral and dorsolateral PFC, the current study investigated audiovisual integration in single units and local cell populations within dorsolateral PFC. Extracellular recordings were collected from three awake, behaving rhesus macaques (Macaca mulatta). Trials were initiated by maintaining central fixation for 1000 ms, after which a visual stimulus appeared centrally on a computer monitor (visual trials), or an auditory stimulus was presented through a speaker located centrally above the monitor (auditory trials), or both visual and auditory stimuli were simultaneously presented (audiovisual trials).

Stimuli included monkey faces and vocalizations, human faces and vocalizations, animal faces and vocalizations, and synthetic visual events and sounds. Each modality format and stimulus type occurred with equal frequency in pseudorandom order. Continuing fixation throughout the entire stimulus period (500 ms) was reinforced on a variable schedule (~20:1) with a calorically dense food reward. Evidence of audiovisual integration within dorsolateral PFC was obtained from units exhibiting significant evoked responses to both auditory and visual stimuli, as well as units with responses to audiovisual stimuli that differed significantly from the maximal unimodal response. The results support an expanded view of the cortical network underlying audiovisual integration, which includes both ventrolateral and dorsolateral divisions of the PFC.

Disclosures: **A. Poremba:** None. **J. Bigelow:** None.

Poster

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Title: Acquiring the multisensory integration capability at maturity

Authors: J. XU[1], L. YU[1], B. A. ROWLAND[2], *B. E. STEIN[2];
[1]Sch. of Life Sci., East China Normal Univ., Shanghai, China; [2]Neurobio. and Anat., Wake Forest Sch. Med., Winston Salem, NC

Abstract: Cat superior colliculus (SC) neurons normally develop the ability to integrate visual-auditory information after 3-4 months of postnatal experience. Restricting visual-auditory experience by rearing them to adulthood in omnidirectional noise disrupts this developmental process (Xu et al., 2014). Prior work demonstrated that multisensory integration capabilities can be acquired later in life with intense training consisting of exposure to concordant cross-modal

cues in a darkened, quiet environment. The aim of the present study was to evaluate whether the cross-modal experience provided by a normal environment would be more effective. Following omnidirectional noise-rearing, animals (n=4) were placed in normal laboratory housing conditions. After 6 months, only 39% (24/61) of the multisensory SC neurons tested had acquired this capacity, a surprisingly low incidence compared to that found in normal controls (77%, 75/97) and dark-reared animals given the intense cross-modal exposure paradigm for 15 weeks (90%, 63/70). The noise-reared animals were then submitted to the same cross-modal exposure paradigm used in dark-reared animals. As before, a progressive increase in the incidence of neurons capable of multisensory integration was noted, and after 32,400 exposure trials (18 experimental sessions), these capabilities appeared to be fully developed. Now the incidence of neurons with multisensory integration capabilities (84%, 56/67) was no longer lower than normal or the rehabilitated dark-reared animals. These results suggest that the mature brain has not lost the capability to develop multisensory integration capabilities, but is less capable of doing so under normal conditions. Presumably, the complexity and ambiguity of cues in the rich, normal environment make it more difficult for the mature brain to extract the needed cross-modal statistics.

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Poster

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Support: Vetenskapsrådet

Kempe Stiftelserna

Title: Functional connectivity between mouse visuo-tactile area RL and cingulate cortex

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Abstract: We have previuosly found that the mouse parietal area RL integrates visual and tactile information in mice (Olcese, Iurilli and Medini, Neuron, 2012). Anatomical work indicates that such area projects to the mouse motor cortex (Wang and Burkhalter, J Neurosci, 2011). Here we

investigate the existence of a functional connection between area RL and the prefrontal cortex of mice by a combination of extracellular and intracellular electrophysiology followed by anatomical identification of recorded neurons. Our data show robust and consistance bimodal field potential responses to unimodal and multisensory stimulation in the projection spot of area RL in the mouse frontal cortex, which are accompanied by intracellular synaptic responses in a relatively sparse population of neurons. This work will be preliminary to elucidate the circuits basis by which the multisensory input coming from RL might facilitate activation of the motor target areas in the prefrontal cortex.

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Poster

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VCU PeRQ

CHIR

Title: Comparison of dendritic spine density/size of primary auditory cortical neurons from early-deaf and hearing cats

Authors: *H. R. CLEMO[1], S. G. LOMBER[2], M. A. MEREDITH[1];
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Abstract: Auditory cortex is reorganized by visual/somatosensory activity following early deafness. These crossmodal inputs arise essentially from the same regions that target the auditory cortices in hearing animals, indicating that crossmodal plasticity is subserved not by the ingrowth of new projections, but by local axonal branching and synapse formation. In areas with a high degree of crossmodal plasticity, concurrent increases in dendritic spine density and diameter have been observed. In contrast, the level of crossmodal plasticity demonstrated within A1 following early deafness remains unresolved. The present study measured dendritic spine features from A1 neurons in early-deaf cats (D; ototoxic administration within the first post-natal month, confirmed by flat ABR) and hearing (H) controls. The auditory cortex of adult cats (D=

3; H=3) was incubated for Golgi-Cox staining. Reactive neurons from A1 were visualized and their dendritic spine features assessed using a light microscope (100x; oil) controlled by Neuroludica software. The overall dendritic spine density (436 dendritic segments) did not vary significantly (D=0.81 spines/μm ± 0.02 se; H=0.82 spines/μm ± 0.005 se). However, spine density significantly decreased in the granular (thalamo-recipient) layers (D=0.42 spines/μm ± 0.02 se; H=0.58 spines/μm ± 0.02 se; $p<0.0001$) but was not changed in the supra- or infragranular layers. The diameter of dendritic spine heads was measured for 3448 spines, revealing that spine heads from early-deaf (D) animals were slightly but significantly larger (D avg. = 0.63 μm ± 0.005 se) than those of their hearing (H) counterparts (H avg. = 0.61 μm ± 0.004 se; $p<0.017$). This increase in spine diameter was exhibited by neurons in the supragranular (D = 0.65 ± 0.007; H= 0.59 ± 0.005; $p<0.001$) and infragranular layers (D = 0.69 ± 0.008; H= 0.63 ± 0.005; $p<0.001$) but not granular (D = 0.44 ± 0.01; H= 0.64 ± 0.01; $p<0.001$) layers, which showed a substantial decrease. These data indicate that dendritic spines in A1 react to early hearing loss in a lamina-dependent manner. Specifically, the presumed reduction of thalamic drive to granular layers corresponds with a large reduction in spine diameter (avg. decrease of 0.2 μm), while the preservation (or perhaps enhancement) of corticocortical inputs corresponds with increased spine diameters (avg. increase of 0.06 μm) in the cortical-recipient layers. When compared with other auditory areas following deafness, these data suggest that crossmodal plasticity employs different synaptic strategies for different regions.

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Poster

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Topic: D.03. Multisensory Systems

Support: NIH Grant DC0007156

Title: Audiovisual integration during short-term memory in primate prefrontal cortex

Authors: *J. BIGELOW[1], A. POREMBA[2];
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Abstract: Audiovisual integration underlies a wide range of adaptive behaviors in humans and other primates, including language and communication. Among the brain regions thought to underlie audiovisual integration is the lateral prefrontal cortex (PFC), which is specialized for

integrating and retaining sensory information in the service goal directed behaviors. Consistent with the ecological importance of audiovisual cues, behavioral studies have reported facilitated learning and enhanced memory for compound auditory-visual stimuli compared to either unimodal component. Nevertheless, neurophysiological investigations of audiovisual integration have traditionally employed passive exposure paradigms, leaving open the question of how circuits underlying audiovisual integration might interact with circuits enabling retention of information beyond periods of direct sensory stimulation. The current study investigated this question by recording neurophysiological activity within PFC during a concurrent audiovisual short-term memory task. Each trial began with a sample stimulus, followed by a retention interval (sample delay), after which a test stimulus was presented. Following a second retention interval (test delay), a button was illuminated to signal the response window. Subjects were trained to press the button following identical (match trials) but not nonidentical stimuli (nonmatch trials). Memoranda comprised sounds for auditory trials, images for visual trials, and sounds plus images for audiovisual trials. Each trial type (match, nonmatch) and modality format (auditory, visual, audiovisual) occurred equally often in pseudorandom order. Audiovisual integration was evident within stimulus periods from units exhibiting significant evoked responses on both auditory and visual trials, and units with responses on audiovisual trials that differed significantly from the maximal unimodal response. Similar forms of audiovisual integration were observed during mnemonic-related responses, including delay activity and differential responses to matching versus nonmatching test stimuli. Additional analyses revealed a dissociation among delay types, wherein inhibitory activity was most likely during sample delays where a behaviorally relevant sensory cue was predicted, excitatory activity was most likely during matching test delays where a motor response was predicted, and no change in activity was most likely during nonmatching test delays where neither event was predicted. The results reveal convergence of cross-modal and cross-temporal integration in individual units and local cell populations within PFC.

Disclosures: **J. Bigelow:** None. **A. Poremba:** None.

Poster

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Title: A cross-modal genetic framework for the organization of sensory pathways

Authors: *D. JABAUDON, G. POUCHELON, L. FRANGEUL, L. TELLEY;
Univ. of Geneva, Geneva, Switzerland

Abstract: Modality-specific sensory inputs from the periphery are processed in parallel in distinct sensory areas of the cortex. For each sensory modality, hierarchical thalamocortical (TC) pathways involving “first-order” (FO) and “higher-order” (HO) thalamic nuclei convey information to the primary and secondary sensory cortical areas, respectively. These conserved circuit properties despite divergent peripheral origins raise the possibility that common developmental genetic programs act across sensory modalities. To explore this possibility, we used transcriptional analysis of distinct sensory TC neurons during circuit assembly. We discover that despite their affiliation to distinct sensory modalities, FO somatosensory, visual, and auditory thalamic neurons are genetically homologous. Moreover, *in vivo* modality-specific manipulation of sensory input revealed an input-dependent induction of FO genes and repression of HO genes. Together, these findings reveal a cross-modal genetic framework for the design and plasticity of sensory TC circuits, providing a unifying logic for the emergence and evolution of parallel sensory pathways.

Disclosures: **D. Jabaudon:** None. **G. Pouchelon:** None. **L. Frangeul:** None. **L. Telley:** None.

Poster

788. Cross-Modal Processing: Neural Circuitry and Development

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 788.14/M5

Topic: D.03. Multisensory Systems

Support: NIH R01-EY014882

Title: Experience dependent plasticity in adult lateral geniculate nucleus

Authors: *J. L. WHITT[1,2], H.-K. LEE[1];
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Abstract: Our laboratory has recently shown that one week of visual deprivation is sufficient to reopen thalamocortical plasticity in adult mice (Petrus, 2014). This finding led us to question canonical limits of thalamic plasticity in adult animals. To test whether sensory experience alters thalamic synapses in adult animals, we preformed whole-cell electrophysiological recordings in

the lateral geniculate nucleus (LGN), medial geniculate body (MGB), and reticular thalamic nucleus (TRN) of three-month old normal reared mice and mice deprived of vision for 1 week. Using a Layer 6 (L6)-Cre mouse line (Ntsr1-Cre), we selectively expressed channelrhodopsin-2 (ChR2) in L6 of the primary visual cortex and recorded evoked excitatory synaptic transmission in the TRN and LGN. We found no change in the strength of cortico-thalamic excitation between normal and visually deprived animals. To test whether thalamic inhibitory strength is altered with sensory experience, we stereotactically injected double-floxed ChR2 (DIO-ChR2) into TRN of parvalbumin-Cre mice to measure the inhibitory synaptic transmission of reticular-thalamic synapses. We found that after visual deprivation, TRN-LGN synapses are significantly stronger and more efficient at following high frequency stimulation, while TRN-MGB inhibitory synaptic strength remains constant. These findings show that the adult thalamus exhibits experience-dependent plasticity specifically by regulating the gain of inhibitory reticular-thalamic synapses. Such plasticity is modality specific in that it is observed in the LGN, but not in the MGB, with visual deprivation. These changes will likely have functional consequences for cross-modal sensory adaptation by shifting thalamic processing towards inputs coming from spared senses.

Disclosures: J.L. Whitt: None. **H. Lee:** None.

Poster

788. Cross-Modal Processing: Neural Circuitry and Development

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 788.15/M6

Topic: D.03. Multisensory Systems

Support: NIH MH 095984

Title: Decoding grapheme-color synesthesia using multivariate pattern analysis

Authors: *R. GOSAVI[1], E. E. MEYERING[2], N. S. ROSE[3], E. M. HUBBARD[1], B. R. POSTLE[2,3];
[1]Educational Psychology, [2]Psychology, [3]Psychiatry, Univ. of Wisconsin- Madison, Madison, WI

Abstract: Synesthesia is a condition in which the stimulation of one sensory modality evokes experiences in a second, unstimulated modality (for a review, see Simner & Hubbard, 2013). In the “grapheme-color” variant, synesthetes reliably, automatically experience a specific color when viewing a specific black-and-white symbol (with different colors associated with different symbols). Previous neuroimaging studies using univariate analyses have shown that synesthesia is associated with activity in color areas, including V4 (for reviews, see Hubbard, 2013; Rouw et

al., 2011; for a critical reveiw, see Hupe, 2015). However, these approaches are inherently unable to address a question of fundamental theoretical interest: Is the subjective experience of synesthetic color generated by the same, or different, neural processes from those that support the perception of veridical color? We have begun to address this question with multivariate pattern analysis (MVPA) by first training a linear classifier to discriminate patterns of brain activity evoked by the visual perception of four different color patches, then attempting to decode activity from separate scanning blocks, during which subjects view black-and-white images of the four letters associated with each of the four colors. Although item level decoding of color was robust for both groups, cross-category decoding was only successful for synesthetes. Finer-grained analysis of confusion matrices derived from MVPA of V1 and of V4 yielded two additional insights. First, consistent with previous studies, the neural coding of color differs qualitatively between these two regions. Second, cross-category decoding in synesthetes is markedly stronger in V4 than in V1. These findings suggest that the synesthetic experience of color may be generated by the same mechanisms that support the visual perception of color. These high-level representations of color, however, may not penetrate "backward" to primary sensory cortex.

Disclosures: **R. Gosavi:** None. **E.E. Meyering:** None. **N.S. Rose:** None. **E.M. Hubbard:** None. **B.R. Postle:** None.

Poster

788. Cross-Modal Processing: Neural Circuitry and Development

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Topic: D.03. Multisensory Systems

Support: Wellcome Trust WT094077MA

ERC AdG 250345

Medical Research Council

Marie Curie IIF 328048

Title: Integration of multisensory inputs by single neurons in the claustrum

Authors: ***A. M. PACKER**, T. YUAN, N. PETTIT, S. CHUN, J. Y. N. LAU, M. HAUSSER; Univ. Col. London, London, United Kingdom

Abstract: The claustrum is a long, thin, bilateral brain region lateral to striatum that is implicated in multisensory and inter-hemispheric coordination of cortical processing. Extensive anatomical work, recently confirmed by high throughput tracing techniques (Zingg et al 2014), indicate widespread connectivity between the claustrum and the cortex and highlight the need for a more thorough investigation of the claustrum's internal elements and integrative properties. For example, do individual neurons in the claustrum integrate multiple inputs, or does multimodal integration occur at the population level via connections between claustral neurons? To address this question, we have employed retrograde and anterograde tracing from mouse primary visual and motor cortex to reliably identify the claustrum in acute slices, enabling whole-cell patch-clamp recordings from confirmed claustral neurons. Recovery of cell morphology with biocytin staining allowed us to assign electrophysiological properties to morphologically-defined claustral cell types. The range of passive membrane properties, action potential waveforms, and degree of spike-frequency adaptation were consistent with previous intracellular recordings in the claustrum of anaesthetized rats. We also employed a channelrhodopsin-based mapping strategy (Petreanu, et al 2007) to activate functional inputs from defined origins onto claustral neurons. Both adapting and fast-spiking neurons received inputs from motor cortex, with strong and fast feedforward inhibition. We validated a dual-color input mapping strategy using Chronos and Chrimson (Klapoetke et al, 2014) to investigate integration of inputs from different cortical sources. Single claustral neurons exhibited responses to selective activation of motor cortex inputs from both ipsi- and contralateral hemispheres. Furthermore, single claustral neurons received functional synaptic input from both ipsilateral somatosensory cortex and contralateral motor cortex. These results indicate that individual claustral neurons perform multimodal integration of sensory inputs. We are currently planning experiments combining imaging and optogenetic stimulation *in vivo* (Packer et al. 2015) to elucidate the function of this elusive brain region.

Disclosures: **A.M. Packer:** None. **T. Yuan:** None. **N. Pettit:** None. **S. Chun:** None. **J.Y.N. Lau:** None. **M. Hausser:** None.

Poster

788. Cross-Modal Processing: Neural Circuitry and Development

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Program#/Poster#: 788.17/M8

Topic: D.03. Multisensory Systems

Support: AASDAP

FINEP

INCT Incemaq

FAPERN

CAPES

CNPq

Title: Neuronal responses in primary somatosensory cortex during a whisker discrimination task

Authors: T. VINHOLO, *A. C. KUNICKI, R. MOIOLI, M. I. SILVA, E. MORYA;
Edmond and Lily Safra Intl. Inst. of Neurosci., Inst. Santos Dumont, Macaiba, Brazil

Abstract: The rat primary somatosensory cortex (S1) has been known to be critically involved in a whisker-dependent tactile discrimination task. To determine how S1 neurons are collectively encoded by populations during the discrimination task we recorded the neural activity of 6 rats Long-Evans during their performance, where animals were trained to discriminate the width of two different apertures (wide versus narrow) using only their large mystacial vibrissae to receive a water reward. We defined a trial as the 2-second period centered around the discriminatory bars. The discrimination happened when there was a beam break upon contact between the bars and whiskers. When the animals achieved a performance of > 75% correct they were implanted bilaterally with an array of 32 electrode channels on each side of S1. The recordings were divided into 3 different time slots: anticipatory (from -0.5 to 0 s), discrimination (from 0 s to 0.3 s) and reward periods (from 0.3 s to 2.0 s). A total of 287 single and multi-units were recorded in 6 behavioral sessions. The firing rates observed in peristimulus time histograms shows that S1 neurons present complex excitatory and/or inhibitory patterns. The formation of specific firing rate patterns within neuronal clusters supported our hypothesis that there is a trend upon different stimuli throughout the task as well as stands to the S1 neurons multimodal property.

Disclosures: **T. Vinholo:** None. **A.C. Kunicki:** None. **R. Moioli:** None. **M.I. Silva:** None. **E. Morya:** None.

Poster

788. Cross-Modal Processing: Neural Circuitry and Development

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Topic: D.03. Multisensory Systems

Support: Kavli Foundation

Norwegian Research Council

Title: Intra-claustral connectivity in the rat measured with voltage sensitive dye imaging

Authors: *A. A. ROBINSON, M. P. WITTER;
Kavli Inst. For Systems Neurosci, CNC, NTNU, Trondheim, Norway

Abstract: The claustrum is a small and highly conserved nucleus that extends rostrocaudally in the forebrain. In the rat, the claustrum is located lateral to the external capsule, bordering the insular and piriform cortices. The claustrum comprises two subregions, the (dorsal) claustrum and the endopiriform nucleus. Previous studies have shown that there are reciprocal connections with many areas of the cortex, however, little is known about the intrinsic connectivity and the function of the claustrum. One hypothesis is that the claustrum is able to synchronize and coordinate the activity of distant cortical areas based on this strong reciprocal connectivity. However, since there is a topographical arrangement of the reciprocal cortical connections of the claustrum, a strong intrinsic network within the claustrum must exist for it to be able to coordinate the activity of distant cortical regions. The current study aimed to investigate the potential intrinsic network within the claustrum and the dorsal endopiriform nucleus of the rat. Connectivity within the claustrum was analyzed with optical imaging, using the voltage sensitive dye (RH-795) in 400 μm thick brain slices from Long Evans rats of 23-30 days old. Sections through the claustrum in both the horizontal and the sagittal planes were used to investigate the connectivity along the anterior/posterior or dorsal/ventral directions respectively. Our results indicate that there is connectivity in all directions tested, with bidirectional activation observed throughout the claustrum and dorsal endopiriform nucleus. More experimental data are needed to confirm the connectivity within and between the claustrum and dorsal endopiriform nucleus and to establish the cells of origin and their postsynaptic targets that form this intrinsic network.

Disclosures: **A.A. Robinson:** None. **M.P. Witter:** None.

Poster

788. Cross-Modal Processing: Neural Circuitry and Development

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 788.19/M10

Topic: D.03. Multisensory Systems

Support: CRSNG

FCI

Title: Effects of enucleation on the direct reciprocal corticocortical connections between the primary visual and somatosensory cortices of the mouse

Authors: *I. O. MASSE, G. BRONCHTI, D. BOIRE;
Anatomie, UQTR, Trois-Rivieres, QC, Canada

Abstract: In the sensory deprived brain, the heteromodal cortical connections appear to play a more significant role in sensory processing (Merabet & Pascual-Leone, 2010). Although some studies report enhanced functional heteromodal cortical connectivity in the blind (Fuji et al., 2009; Klinge et al., 2010), others report a contradictory finding of decreased functional connectivity of the visual cortex in blind subjects (Liu et al., 2007; Yu et al., 2008). The purpose of this study is to compare the direct reciprocal corticocortical intermodal connections between the primary visual cortex (V1) and the primary somatosensory cortex (S1) in intact and C57BL/6 mice enucleated at birth, and to determine quantitative differences in the strength and laminar distribution of neurons and terminals in these projections. MATERIALS AND METHODS: In adult mice, iontophoretic injections of high molecular weight biotinylated dextrans (10kDa) and of the B fragment of cholera toxin (CTB) were performed in V1 and in S1 of intact and mice enucleated at birth. Axonal swellings were sampled using the software Stereo Investigator (MBF Bioscience). The size of swellings was measured and the frequency distribution was determined for each cortical layer. CTB retrogradely labeled neurons were used to estimate the relative weight of the projections between V1 and S1, and their laminar distribution was used to classify the projections as feedback, feedforward or lateral. RESULTS: Injections of CTB in V1 resulted in a greater proportion of labeled cells in the barrel field of intact mice than of enucleated mice. Following injections of BDA in V1, a greater range of axonal swelling size was observed in S1 of intact mice compared to enucleated mice. Large axonal swellings were observed in all cortical layers in S1 of intact mice whereas only small swellings were observed in enucleated mice. Injections of CTB and BDA in S1 of enucleated mice, however, resulted in no significant differences from intact mice. CONCLUSION: In the enucleated mice, the projection from V1 to S1 appears to play a different role in sensory processing. The absence of larger axonal swellings in the projection from V1 to S1 of enucleated mice strongly suggests that S1 no longer receives the Class 1 B driver inputs from V1 which were found in intact mice and that V1 inputs to S1 now have a predominant modulatory influence. This study provides evidence for alterations in heteromodal connections through anatomical changes following visual deprivation.

Disclosures: I.O. Masse: None. **G. Bronchti:** None. **D. Boire:** None.

Poster

788. Cross-Modal Processing: Neural Circuitry and Development

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Program#/Poster#: 788.20/M11

Topic: D.03. Multisensory Systems

Support: Florida Atlantic University

Title: Pruritic (itch) response in the nervous system of *Drosophila* melanogaster

Authors: *C. JOHN, R. K. MURPHEY, K. DAWSON-SCULLY, J. R. NAMBU;
Biol. Sci., Florida Atlantic Univ., Jupiter, FL

Abstract: Pruritus, or itch, is an unpleasant sensation that evokes an intense desire to scratch. Itch can be classified as an acute or chronic condition. Acute itch typically results from a bite or sting and can serve as a protective mechanism against tissue damage caused by parasites. However, chronic itch can occur when the immune and/or nervous systems dysfunction. It can also result from the dysregulation of itch and pain signaling. In mammals, pruritogens, or itch inducing agents, stimulate peripheral unmyelinated c-fiber pruriceptors, which are pruritogen detecting primary sensory neurons in the skin, causing transmission of sensory input to interneurons and projection neurons of the brainstem via the spinothalamic tract. This induces the itch sensation in the brain and the subsequent scratching behavior. Pruritic mediators include nerve growth factors, serotonin, endothelin-1 and TNFα, among numerous others. Commonly studied pruritogens include histamine, which is released during mast cell degranulation; compound 48/80, which induces histamine release; cowhage spicules, which signal a histamine-independent pathway and Chloroquine, an antimalarial drug for which itch is a side effect. Itch is a primary symptom in patients with skin diseases and systemic and metabolic disorders, including liver and kidney diseases, HIV and AIDS, brain cancer. It is also seen in psychiatric disorders like anxiety, depression, schizophrenia and delusions of parasitosis, which leads to self-injurious behavior. Since treatments currently available are ineffective in treating most cases of pruritus, elucidation of the mechanisms that underlie this condition using *Drosophila* will allow for identification of more specific anti-itch treatments. In current study, we are developing *Drosophila* as a model organism for investigating pruritus. To analyze the effects of pruritogens on *Drosophila* behavior, we administer aerosolized pruritogens, allowing the pruritogen to be taken up through their cuticle and spiracles. Our preliminary results indicate that both Histamine and Compound 48/80 evoke a significant behavioral response in flies resulting in longer grooming bout duration, compared to the control flies. However, Chloroquine and cowhage do not appear to significantly affect the flies' grooming behavior. Since some of the pruritogens tested evoked a response in the flies, while others did not, we believe the behavioral response we observed was a pruritic response. Therefore, based on these findings, we conclude that

Drosophila can indeed be used as a model organism for investigating pruritus and that both vertebrates and invertebrates experience itch.

Disclosures: C. John: None. **R.K. Murphey:** None. **K. Dawson-Scully:** None. **J.R. Nambu:** None.

Poster

788. Cross-Modal Processing: Neural Circuitry and Development

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Topic: D.03. Multisensory Systems

Support: James S. McDonnell Foundation Scholar Award

Title: Transcriptional profiles of supragranular-enriched genes predict corticocortical network architecture in the human brain

Authors: *F. M. KRIENEN[1], B.-T. T. YEO[2], C. J. CHARVET[1], R. L. BUCKNER[3], C. C. SHERWOOD[1];
[1]The George Washington Univ., Washington, DC; [2]Electrical and Computer Engin., Natl. Univ. of Singapore, Singapore, Singapore; [3]Harvard Univ., Cambridge, MA

Abstract: The human brain is patterned with distributed networks that connect a disproportionately large cerebral cortex across multiple association zones in the frontal, temporal and parietal lobes. The expansion of the cortical surface, along with the emergence of new cortical areas and long-range connectivity networks, may be reflected in changes to the underlying molecular architecture. Using the Allen Institute's transcriptional atlas of the human brain, we demonstrate that genes that are particularly enriched in supragranular layers in the human cerebral cortex relative to mouse (Zeng et al. 2012) are correlated with large-scale network organization measured by functional connectivity MRI (Yeo et al. 2011). Candidate genes focused on those that are preferentially expressed in human upper layers (layers II/III), while in mouse are enriched in deep layers (layers V/VI). Microarray expression data for candidate genes from postmortem human brains (n=6) were cross-correlated to identify molecular profiles for each available cortical location. These were then clustered according to consensus maps of human functional connectivity networks (7 or 17 cortical networks, n=1000; Yeo et al. 2011). Results indicate that regions falling within sensory and motor zones have similar molecular profiles, despite being distributed across the cortical mantle. Sensory and motor region profiles were also anti-correlated with the profiles of limbic and association

regions. Alternate gene sets were tested, including, (1) using gene sets with annotated functional ontologies related to connectivity in mice (Wolf et al. 2011), (2) genes that are cortically enriched relative to subcortical structures (Konopka et al. 2012), and (3) genes with non-specific laminar distributions. Gene sets with conserved functional ontologies related to connectivity dissociated sensory and motor regions from limbic and association regions, but to a significantly lesser extent than the upper layer enriched set. Immunohistochemical and *in situ* hybridization expression data in nonhuman primates, including New World monkeys, Old World monkeys and apes, indicates that supragranular enrichment of these genes is not uniform across all primates. Molecular innovations of upper layer cortical architecture may be an important component in the evolution of increased long-range corticocortical projections across primates.

Disclosures: F.M. Krienen: None. **B.T. Yeo:** None. **C.J. Charvet:** None. **R.L. Buckner:** None. **C.C. Sherwood:** None.

Poster

788. Cross-Modal Processing: Neural Circuitry and Development

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Topic: D.03. Multisensory Systems

Support: AG received a Post-doc fellowship from the Alexander von Humboldt Foundation

Title: Principles of ipsilateral and contralateral cortico-cortical connectivity in the mouse

Authors: *A. GOULAS[1,2], H. B. M. UYLINGS[3], C. C. HILGETAG[1,4];
[1]Uke/Institute For Computat. Neurosci., Hamburg, Germany; [2]Max Planck Res. Group Neuroanatomy and Connectivity, Max Planck Inst. for Human Cognitive and Brain Sci., Leipzig, Germany; [3]Dept. of Anat. and Neurosci., VU Univ. Med. Ctr., Amsterdam, Netherlands; [4]Dept. of Hlth. Sci., Boston Univ., Boston, MA

Abstract: Structural connectivity among areas of the cerebral cortex provides the substrate for information exchange and is characterized by systematic patterns of presence or absence of connections between specific areas. Such pattern results in a topology that is essential for functional features characterizing healthy brain functioning. What principles govern this cortical wiring diagram? Building on prior work in the cat and macaque cortex (Beul et al., 2014a; 2014b) we investigated the relation of physical distance and cytoarchitecture with the connectional architecture of the mouse cortex and the organization of ipsilateral and contralateral connections. We use two independent datasets that constitute the current best estimate of mouse

cortico-cortical connectivity (Oh et al. 2014; Zingg et al. 2014). First, we reveal a mirrored and attenuated organization of ipsilateral and contralateral connections. Second, both physical distance and cytoarchitecture significantly relate with the presence and absence of connections. Notably, this analysis demonstrated that: i) Both factors conjointly relate better to the mouse cortico-cortical pattern than the contribution of each factor in isolation. ii) The two factors contribute differently to ipsilateral and contralateral connectivity. While physical distance, when compared to cytoarchitecture, is more tightly related to the presence or absence of ipsilateral connections, the opposite holds for the contralateral connections. The current results, conjointly with findings for the cat and macaque cortex, suggest that despite the striking differences of mouse, cat and macaque brains across space (brain size) and time (phylogenetic scale), common principles seem to pertain to the wiring of these systems. The identified wiring principles offer a guiding thread for unveiling neurobiological mechanisms that result in the close relation between the physical, cytoarchitectonic and connectional architecture of the brain. Beul SF, Grant S, Hilgetag CC (2014a) A predictive model of the cat cortical connectome based on cytoarchitecture and distance. Brain Struct Funct. doi:/10.1007/s00429-014-0849-y Beul SF, Barbas H, Hilgetag CC (2014b) A predictive model of the primate cortical connectome based on cytoarchitecture and physical distance. 20th Annual Meeting of the Organization for Human Brain Mapping, Hamburg, Germany. Oh SW et al. (2014) A mesoscale connectome of the mouse brain. Nature 508:207-214. Zingg B, Hintiryan H, Gou L, Song MY, Bay M, Bienkowski MS, Foster NN, Yamashita S, Bowman I, Toga AW, Dong H-W (2014) Neural networks of the mouse neocortex. Cell 156:1096-1111.

Disclosures: **A. Goulas:** None. **H.B.M. Uylings:** None. **C.C. Hilgetag:** None.

Poster

788. Cross-Modal Processing: Neural Circuitry and Development

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Topic: D.03. Multisensory Systems

Support: NIH Grant EY016716

NIH Grant EY022458

Title: Multisensory plasticity in the superior colliculus: different rules for time and space

Authors: ***C. DONG**, B. E. STEIN, B. A. ROWLAND;
Dept. of Neurobio. and Anat., Wake Forest Univ. Sch. of Med., Winston Salem, NC

Abstract: The physiological products of multisensory integration in the deep layers of the superior colliculus (SC) are dependent on the spatial and temporal configurations of cross-modal cues. Whereas spatially and temporally concordant cross-modal cues typically elicit responses that are more robust than the component cues (multisensory enhancement), spatially and/or temporally disparate cues elicit responses that are weaker (multisensory depression). These spatial and temporal principles of multisensory integration are popularly summarized as a singular "spatiotemporal principle", according to which concordance yields enhancement and discordance yields depression. The aim of the present study was to evaluate whether the similarity evident in the tuning of the multisensory process to spatial and temporal displacement was echoed in the sensitivity of this tuning to short-term sensory experience. In short, the question was whether the presumptive plasticity of the system was equivalent across space and time. Adult SC neurons were repeatedly presented with many (100) exposure trials of visual-auditory (VA) cues that were in one of 3 configurations: (a) spatiotemporally concordant (same location, V leading A by 50ms), (b) spatially disparate (V inside and A outside its receptive field), or (c) temporally disparate (V leading A by 100ms or 150ms). Responses were compared to baseline measures taken before exposure. The data revealed that this short-term experience could alter the temporal preferences of many neurons, but had little effect on their spatial preferences. In many cases neurons switched their temporal preferences toward the disparity presented in the exposure trials. In contrast, neither exposure to spatially concordant nor spatially disparate configurations induced reliable changes in the multisensory products of their synthesis. These results reveal an asymmetry in the short-term plasticity of the spatial and temporal principles of multisensory integration. Furthermore, they suggest that there are different rules for incorporating these principles during development, and for maintaining or adapting them to changes in environmental conditions.

Disclosures: **C. Dong:** None. **B.E. Stein:** None. **B.A. Rowland:** None.

Poster

788. Cross-Modal Processing: Neural Circuitry and Development

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Topic: D.03. Multisensory Systems

Support: NIH AA022455

NIH AA13023

Title: Multisensory functional connectivity is present in the neonate cortex

Authors: *A. E. MEDINA[1], C. SOURS[2], P. RAGHAVAN[3], W. FOXWORTHY[1], J. ZHUO[3], D. EL-METWALLY[1], M. MEREDITH[4], J. GILMORE[5], R. P. GULLAPALLI[2];
[1]Dept of Pediatrics, [2]Dept. of Diagnos. Radiology and Nuclear Medicine; Magnetic Resonance Res. Ctr., [3]Dept. of Diagnos. Radiology and Nuclear Med., Univ. of Maryland, Sch. of Med., Baltimore, MD; [4]Anat. and Neurobio., Virginia Commonwealth Univ., Richmond, VA; [5]Psychiatry, Univ. of North Carolina, Chappel Hill, NC

Abstract: Although the developmental trajectory of multisensory processing has long intrigued scientists, contrasting views have been proposed for its ontogeny. One view, posits that the different unimodal sensory modalities are segregated at birth and multisensory processing occurs only after appropriate postnatal experience. An alternate view argues that newborns are born with multisensory connectivity which becomes refined and segregated by sensory experience. To assess whether humans exhibit crossmodal connectivity at term (birth) or not, we used resting state fMRI to evaluate the corticocortical connectivity of two areas known to be multisensory in adults: the Intraparietal Sulcus (IPS; a region of largely visual-somatosensory convergence) and the Superior Temporal Sulcus (STS; a region of largely visual-auditory convergence). Data for term infants were obtained from University of North Carolina, Chapel Hill (UNC cohort, n=9) and from University of Maryland, Baltimore (UMD cohort, n=6), each of which revealed no structural anomalies on MRI and performed within the normal range on a comprehensive neurological examination. The rsfMRI results demonstrated, that there was significant functional connectivity at term of the IPS with visual association (MT, V3) and somatosensory association areas (S3), which is similar to the connectivity of the adult IPS. Similarly, the STS in newborn infants showed significant functional connectivity with the visual association areas (MT, V4), primary auditory cortex (A1) and, to a lesser degree, the somatosensory association areas (S2 and S3), which mirrors the pattern of adult connectivity. Thus, rsfMRI provides convincing evidence that both the IPS and STS areas already display functional communication with multiple sensory cortices at birth. These data are consistent with demonstrations of multisensory processing in human newborns that can visually recognize objects previously explored only by touch, or that have visual perceptions modified by the presence of an auditory stimulus. Collectively, these observations support the multisensory at birth view of sensory ontogeny.

Disclosures: A.E. Medina: None. **C. Sours:** None. **P. Raghavan:** None. **W. Foxworthy:** None. **J. Zhuo:** None. **D. El-Metwally:** None. **M. Meredith:** None. **J. Gilmore:** None. **R.P. Gullapalli:** None.

Poster

789. Architecture of Extrastriate Cortex

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Support: NIH EY 16187

NIH EY 24187

P41EB015896

S10RR021110

Title: The functional development of macaque inferotemporal cortex

Authors: *J. L. VINCENT, K. SRIHASAM, M. LIVINGSTONE;
Neurobio., Harvard Med. Sch., Boston, MA

Abstract: Primate inferotemporal cortex is subdivided into domains for biologically important categories, such as faces, bodies and scenes. How this organization comes about is unknown. To monitor the normal development of category selective domains we collected functional MRI on five normally developing infant macaques while they passively viewed movies and images of faces and objects in the scanner. We have developed techniques for safely and non-invasively doing functional MRI in alert infant macaques and have longitudinally scanned monkeys from as early as 7 days old. Our results indicate that the development of visual responsiveness in IT proceeds from early, posterior, visual areas towards anterior IT. The youngest monkeys (1-2 weeks old) showed visually evoked signal only in LGN and the superior colliculi. Early visual areas and inferotemporal cortex did not show significant signal change to visual stimulation until approximately 1.5 and 3 months of age, respectively. This slow maturation is surprising in light of reported early maturity of single unit responsiveness in both V1 (Wiesel & Hubel, 1974) and IT (Rodman et al. 1993); we do not know whether this delay represents immaturity of vascular responsiveness or the physiology of neuronal populations. Category-selective responses to faces or object stimuli were first observed in the superior temporal sulcus and middle temporal gyrus at approximately 6-7 months of age.

Disclosures: J.L. Vincent: None. **K. Srihasam:** None. **M. Livingstone:** None.

Poster

789. Architecture of Extrastriate Cortex

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 789.02/M17

Topic: D.04. Vision

Support: NIH Intramural

Title: The amygdala is causally connected to the superior temporal sulcus (STS) for dynamic face perception

Authors: *D. PITCHER, S. JAPEE, L. UNGERLEIDER;
NIH/NIMH, Bethesda, MD

Abstract: Non-human primate neuroanatomical studies demonstrate that a cortical pathway from the superior temporal sulcus (STS) projects into the dorsal regions of the amygdala but whether this same connection exists in human cortex remains unclear. In the present study we addressed this question by combining thetaburst transcranial magnetic stimulation (TBS) with functional magnetic resonance imaging (fMRI) to causally test the prediction that the STS and the amygdala are functionally connected for processing the dynamic aspects of faces. Participants (N=22) were scanned over two sessions while viewing 3-second video clips of faces, bodies and objects. During these sessions, TBS was delivered over the right posterior superior temporal sulcus (rpSTS) or the vertex, a point on the top of the head that acted as a TMS control site. A region of interest (ROI) analysis revealed results consistent with our hypothesis. Namely, TBS delivered over the rpSTS reduced the BOLD response to faces and bodies (but not objects) in the rpSTS itself and the BOLD response to faces in the amygdalae bilaterally when compared with TBS delivered over the vertex control site. These results causally demonstrate that the rpSTS is functionally connected to the amygdala for the perception of dynamic faces.

Disclosures: **D. Pitcher:** None. **S. Japee:** None. **L. Ungerleider:** None.

Poster

789. Architecture of Extrastriate Cortex

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Program#/Poster#: 789.03/M18

Topic: D.04. Vision

Support: NSERC IDG

Connaught New Researcher Award

Title: Feature derivation and facial image reconstruction from patterns of neural activation

Authors: *A. NESTOR[1], D. NEMRODOV[1], D. PLAUT[2], M. BEHRMANN[2];
[1]Univ. of Toronto Scarborough, Scarborough, ON, Canada; [2]Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Recent attempts at neural-based image reconstruction, including facial image reconstruction, have established the ability of BOLD patterns to support this enterprise. However, these attempts rely on prespecified image features motivated by their general biological plausibility. Here, we take on the twofold task of deriving features directly from patterns of neural activation and of using those features for the purpose of face reconstruction. To be clear, reconstruction serves here both as a goal in itself and as a means of validating the visual code underlying neural face representations in the context of an assumption-sparse methodological framework. More specifically, we use a version of reverse correlation to derive facial features from patterns of activation in high-level visual areas and, then, we combine those features linearly to reconstruct novel face images from the activation that they elicit. This approach allows us to estimate an entire gallery of visual features associated with different cortical areas as well as to achieve significant levels of reconstruction accuracy as confirmed both by objective image metrics and by psychophysical data. Furthermore, we show how this approach can be immediately extended to both behavioral data and to other neuroimaging modalities (e.g., EEG). From a theoretical perspective, the present findings provide key insights into the nature of high-level visual representations and into their reliance upon specific neural resources (e.g., cortical areas, frequency bandwidths). At the same time, they open up the possibility of a broad range of image-reconstruction applications via a straightforward methodological approach.

Disclosures: **A. Nestor:** None. **D. Nemrodov:** None. **D. Plaut:** None. **M. Behrmann:** None.

Poster

789. Architecture of Extrastriate Cortex

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Program#/Poster#: 789.04/M19

Topic: D.04. Vision

Support: NIMH IRP

Title: Temporal integration windows of AF face patch neurons using naturalistic movies

Authors: *B. E. RUSS, J. DAY-COONEY, D. A. LEOPOLD;
Section on Cognitive Neurophysiol. and Imaging, Lab. of Neuropsychology, NIMH/NIH, Bethesda, MD

Abstract: Previous studies have shown that a region of the anterior superior temporal sulcus of the rhesus macaque, the anterior fundus face patch (AF), is selective for faces. These studies most often involve the presentation of static images flashed in a subject's center of gaze for a few hundred milliseconds. Recent studies have begun probing AF and related areas with more ethologically relevant paradigms, using dynamic presentations of real world stimuli. Work from our lab has shown that individual neurons in AF respond in a consistent manner to the content of dynamic movies during free viewing. Although we found selectivity for flashed faces in most neurons, responses were weakly tied to the appearance of faces in the video. Many adjacent neurons were uncorrelated in their responses to natural videos. These results raise a set of challenging questions about how neurons in face patches process visual information under natural conditions. For example, to what extent do AF neurons integrate temporal information in their responses? Here we addressed this question using chronically implanted 64-channel microwire bundles in two rhesus macaques in the AF face patch. We recorded neural activity longitudinally from single units, isolated over several weeks, while interleaving a number of different tasks each day. In a fixation task, we assessed selectivity to a set of six static image categories. In a natural viewing task, we measured responses to several social movies, depicting interacting conspecifics interacting, as well as "non-social control" movies with no animals present. Additionally, we presented short movie clips, sampled at one-second intervals from one of the social movies and shown in random order. We varied the duration of the clips to systematically investigate the temporal response integration of AF cells. By arranging the randomly presented clips in their original chronology and comparing the reordered neural responses to those obtained during continuous viewing, we assessed the temporal integration properties of single AF neurons. Using this method, we found that temporal features elapsing over approximately 500ms shaped the responses of most neurons in this area. Mixed in with this population were neurons whose responses did not obviously depend on temporal information, as the reordered responses to flashed static images and brief clips closely resembled responses from continuous viewing. The categorical selectivity of individual neurons to flashed stimuli was not a reliable predictor of the cells' dependence on temporal integration. These results demonstrate the inherent response heterogeneity of "face cells" in the context of natural vision.

Disclosures: B.E. Russ: None. **J. Day-Cooney:** None. **D.A. Leopold:** None.

Poster

789. Architecture of Extrastriate Cortex

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Topic: D.04. Vision

Support: European Research Council (ERC-2011-Stg-284101)

federal research action (IUAP-P7/11)

Title: Dissociations and associations between shape and category representations in the two visual pathways

Authors: *S. BRACCI, H. OP DE BEECK;
Lab. voor Biologische Psychologie, KU Leuven, Leuven, Belgium

Abstract: Both visual pathways represent visual and conceptual object properties. Recent reports tried to explain conceptual representations by referring to visual properties, but without dissociating the two alternatives. We present an event-related fMRI study that explicitly dissociates shape from category in order to investigate their independent contribution as well as their interactions through representational similarity analyses. Results reveal an independent contribution from each dimension in both streams, with a transition from shape to category along the posterior-to-anterior anatomical axis. The nature of these shape-independent category representations differs in the two pathways: ventral areas represent object animacy and dorsal areas represent object action properties. Furthermore, information about shape evolved from low-level to high-level shape following a posterior-to-anterior gradient similar to the shape-to-category emergence. To conclude, representations of shape and category independently coexist and interact throughout the visual hierarchy, as such reconciling visual and semantic accounts of the visual system functional organization.

Disclosures: S. Bracci: None. **H. Op de Beeck:** None.

Poster

789. Architecture of Extrastriate Cortex

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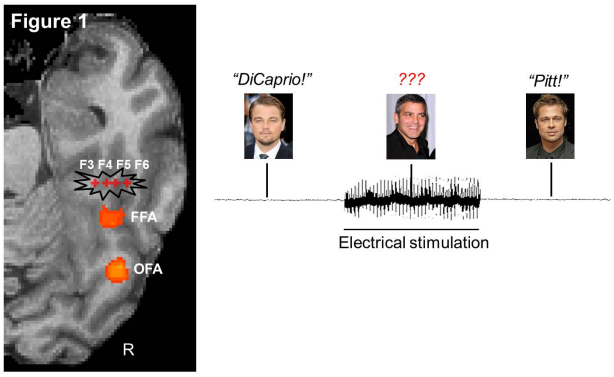
Topic: D.04. Vision

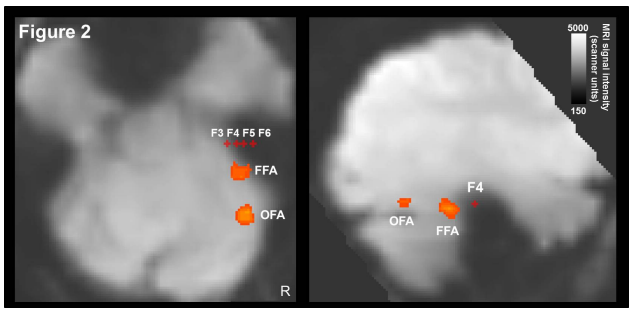
Support: ERC grant (facessvep 284025)

Title: Beyond the core face-processing network: intracerebral stimulation of a face-selective area in the right anterior fusiform gyrus elicits transient prosopagnosia

Authors: *J. JONAS[1], L. MAILLARD[2], H. BRISSART[2], B. ROSSION[1];
[1]Catholic Univ. of Louvain, Louvain-la-Neuve, Belgium; [2]Univ. Hosp. of Nancy, Nancy, France

Abstract: According to neuropsychological evidence, a distributed network of face-selective regions of the ventral visual pathway supports face recognition. However, fMRI studies have generally confined to the posterior face-selective areas, i.e., the occipital face area (OFA) and the fusiform face area (FFA). There is recent evidence that intracranial electrical stimulation of the OFA and FFA elicits face recognition impairments. Here we were able to test for face recognition in a patient implanted with depth electrodes in the anterior temporal cortex. Electrically stimulating the right anterior fusiform gyrus, in a region located anteriorly to the FFA, induced a transient inability to recognize familiar faces (Fig. 1, stimulation of electrodes F3, F4, F4 and F6; movies available). This region was shown face-selective as revealed by intracerebral face-selective event-related potentials and gamma band activity recorded at these critical electrodes. However, no fMRI face-selective responses were found in this region due to severe BOLD signal drop-out caused by the ear canal artifacts (see raw EPI slices, Fig. 2). These results point to a causal role in face recognition of the right anterior fusiform gyrus and more generally of face-selective areas located beyond the "core" face processing network in the ventral temporal cortex. It also illustrates the diagnostic value of intracerebral recordings and stimulation in understanding the neural basis of face recognition and visual recognition in general





Disclosures: **J. Jonas:** None. **L. Maillard:** None. **H. Brissart:** None. **B. Rossion:** None.

Poster

789. Architecture of Extrastriate Cortex

Location: Hall A

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Topic: D.04. Vision

Support: Israeli Science Foundation

Title: Two neural pathways of face processing: An updated model

Authors: M. BERNSTEIN[1], J. ORON[1], *G. YOVEL[2];
[1]Sagol Sch. of Neurosci., [2]Tel Aviv Univ., Tel Aviv, Israel

Abstract: Faces elicit selective neural responses in various brain areas. According to current neural face models (Haxby et al., 2000, 2007) brain areas responsive to faces are divided into core face areas and extended face areas. The core face areas extract visual information from faces and include the face-selective areas in the lateral occipital cortex (occipital face area - OFA), the fusiform gyrus (fusiform face area - FFA) and the posterior superior temporal sulcus (pSTS face area - pSTS-FA). Furthermore, there is a division of labor between the core areas such that the FFA extracts invariant aspects of faces (e.g. identity, gender) and the pSTS represents changeable facial aspects (e.g., expression, gaze). The extended face areas are not selective to faces but are responsive to face-related information such as speech, semantic & emotional information. This dominant model is primarily based on studies that presented static images of faces. Recently we have started examining the neural representation of dynamic faces and reveal several new findings that call for an updated neural model. First, dynamic faces generate face-selective activations in additional areas not included in the original model in the anterior STS (aSTS) and the inferior frontal gyrus (IFG). Second, the primary division of labor between the ventral and dorsal face areas is to form and motion, rather than to invariant and changeable aspects. Specifically, the OFA and FFA do not extract additional information from dynamic than static faces, whereas the STS is highly responsive to dynamic facial information regardless of whether subjects are performing an expression (changeable) or gender (invariant) task. Third, the dorsal face areas are not only selective to dynamic faces but are highly selective to human voices (e.g., cry, laugh, cough) relative to non-human sounds (e.g. ring, beep), whereas the ventral face areas are not responsive to human voices. Taken together our results as well as additional recent findings in the literature, we suggest an updated model according to which the neural face network is composed of two main pathways, a ventral pathway, which is unimodal

and extracts form information from both invariant and changeable aspects of faces and a dorsal pathway, which is multimodal and extracts dynamic visual and auditory information about people.

Disclosures: **M. Bernstein:** None. **J. Oron:** None. **G. Yovel:** None.

Poster

789. Architecture of Extrastriate Cortex

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Support: NIH Grant EY020484

Title: Deep neural networks models predict spatio-temporal cortical dynamics of visual object recognition

Authors: ***A. OLIVA**[1], A. KHOSLA[1], D. PANTAZIS[2], A. TORRALBA[2], R. M. CICHY[2]; [1]CSAIL, [2]MIT, Cambridge, MA

Abstract: The cortical basis of visual object recognition in humans is a rapidly unfolding, complex multistage process in space and time whose understanding necessitates a model capturing its complexity. A major impediment in creating such a model is the highly nonlinear and sparse nature of neural tuning properties in mid- and high-level visual areas, precluding principled understanding. We propose a framework that obviates this impediment by comparing brains to deep convolutional neural networks (CNN), i.e. computer vision models whose model neural tuning properties are set during supervised learning without manual intervention (Fig. 1a). We recorded MEG and fMRI data in 15 participants while those viewed images of 118 images (Fig. 1b). Using representational similarity analysis, we compared brain responses to a state-of-the-art CNN trained on object categorization (object-CNN). By comparison of MEG data to the CNN, we showed that each layer of the object-CNN predicted brain representations (Fig. 1c), and the relationship was hierarchical: low layers of the CNN correlated with MEG early in time, and high layers later (Fig. 1d). By comparison of fMRI data to the CNN using a spatially unbiased searchlight approach, we showed that CNNs predict visual representations in the ventral, but also the dorsal stream, providing novel support for object representations in parietal cortex independent of motor movement or attentional confounds. Together, our results provide a novel, algorithmically explicit perspective on the nature of visual object recognition in the human brain in the first few hundred milliseconds of vision.

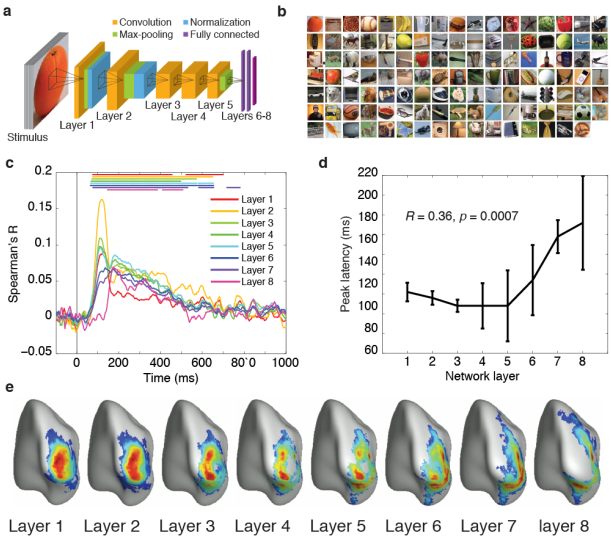

Figure 1. a) The Convolutional neural network (CNN) had an 8-layer architecture, implementing biologically plausible operations such as convolution, max pooling and normalization. **b)** The image set consisted of 118 images of real-world objects on natural backgrounds. **c)** All layers of the CNN predicted MEG responses with different time courses. **d)** There was a temporal hierarchical relationship between network layer position and peak latency of the layer-specific MEG time courses: the higher the CNN layer, the later the peak in predicting MEG responses (R=0.36, p= 0.0007). **e)** We found a spatial hierarchical relationship between network layer position and cortical regions, too: while low layers predicted fMRI activity in the occipital pole, higher layers predicted activity in more anterior regions along both the ventral and dorsal visual stream.

Disclosures: **A. Oliva:** None. **A. Khosla:** None. **D. Pantazis:** None. **A. Torralba:** None. **R.M. Cichy:** None.

Poster

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QZ is a postdoctoral fellow of the FWO-Flanders

Title: Functional correspondence between human and monkey face-selective regions in processing face configuration

Authors: *Q. ZHU[1], M. SPRONK[1], W. VANDUFFEL[1,2,3];
[1]Lab. For Neuro- and Psychofysiology, K.U. Leuven, Leuven, Belgium; [2]Dept. of Radiology, Harvard Med. Sch., Boston, MA; [3]A.A. Martinos Ctr. for Biomed. Imaging, Massachusetts Gen. Hosp., Charlestown, MA

Abstract: The monkey plays a critical role in understanding the neural mechanisms of face perception. However, it is unclear whether monkeys process faces in a similar holistic manner as humans and how monkey and human face-selective regions correspond. To address this, we performed the same fMRI experiment in these two species. We presented human face parts in either their normal composition or deviant compositions in different blocks. Veridical and scrambled faces were created by disassembling the same composite images (four veridical faces positioned around a fixation point) in two different ways. We either presented each full set of face features from one of the four veridical faces separately, or spread them over the four faces (hence showing four different features from the four different faces). This resulted in scrambled faces that fully controls for local low-level stimulus differences compared to the veridical faces while destroying the veridical configurations. To further control for different degrees of stimulus spreading and asymmetry, we created two other conditions with face features arranged in a scrambled configuration at each of the four positions in the initial composite images. Finally, two additional control conditions were created with objects instead of face parts. Three monkeys and twenty humans were scanned while they performed a fixation task. An independent localizer experiment was performed in the same subjects to identify face-selective regions. We found a significant face configuration effect in monkey face-selective regions PL, ML, MF and lMFa, and in human OFA, FFA, rpSTS and rmSTS. In addition, compared to the spreaded version, the scrambled faces and objects elicited a significantly lower response in monkey PL and ML, and in human OFA and FFA, likely due to surround suppression in the latter stimuli, whereas the same contrast revealed a significant positive activation in monkey MF and lMFa, and in human rmSTS. In PL and OFA, the veridical faces elicited a similar response as their spreaded version, whereas the veridical faces elicited a significantly higher response in FFA and all the other regions, suggesting a correspondence between PL/OFA. Furthermore, through an inter-species multiple voxel representational similarity analysis, we found that the pattern dissimilarity between the four types of faces in human rmSTS is more similar to that in monkey MF and rAF, whereas the pattern dissimilarity in human OFA, FFA and rpSTS is more similar to that in monkey PL and ML. Taken together, these results suggest a similar face processing system between humans and monkeys, with possible functional correspondences between PL/OFA, ML/FFA and MF/rmSTS.

Disclosures: **Q. Zhu:** None. **M. Spronk:** None. **W. Vanduffel:** None.

Poster

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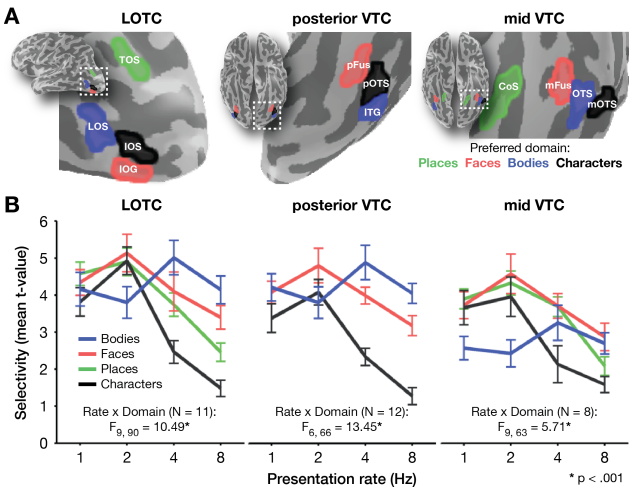
Support: NIH Grant 1R01EY02391501A1

Title: Temporal processing capacity in high-level visual cortex is domain-specific

Authors: *A. STIGLIANI, K. S. WEINER, K. GRILL-SPECTOR;
Psychology, Stanford Univ., Stanford, CA

Abstract: Prevailing hierarchical models propose that temporal processing capacity - the amount of information that a brain region processes in a unit time - decreases at higher stages in the ventral stream. However, it is unknown if high-level visual regions have temporal processing capacities that are domain-general or domain-specific. Using a novel fMRI paradigm, we estimated the temporal capacity of functional regions across the human ventral stream. Contrary to hierarchical models predicting domain-general capacities, our data reveal domain-specific processing capacities: (1) regions processing information from different domains have differential temporal capacities within each stage of the visual hierarchy and (2) regions processing the same domain display the same temporal capacity irrespective of their position in the processing hierarchy. In general, character-selective regions have the lowest capacity, face- and place-selective regions have an intermediate capacity, and body-selective regions have the highest capacity. Notably, cortical temporal processing capacities are not inherited from V1 and have perceptual implications. Behavioral testing revealed that the encoding capacity of body images is higher than that of characters, faces, and places and there is a correspondence between peak encoding rates and cortical capacities for characters and bodies. The present evidence supports a model in which the natural statistics of temporal information in the visual world guides domain-specific temporal processing and encoding capacities. These findings suggest that the functional organization of high-level visual cortex may be constrained by temporal characteristics of stimuli in the natural world, and this temporal capacity is a characteristic of domain-specific networks in high-level visual cortex.



Disclosures: **A. Stigliani:** None. **K.S. Weiner:** None. **K. Grill-Spector:** None.

Poster

789. Architecture of Extrastriate Cortex

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Topic: D.04. Vision

Support: NIH Grant EY023067

Title: The functional organization of early and higher-order visual cortex in patients with lobectomy/hemispherectomy

Authors: ***M. BEHRMANN**[1], T. LIU[2], A. NESTOR[3], K. KAY[4], M. VIDA[2], J. A. PYLES[2], X. ZHANG[5], C. PATTERSON[6];
[2]Ctr. for the Neural Basis of Cognition, [1]Carnegie Mellon Univ., Pittsburgh, PA; [3]Psychology, Univ. of Toronto, Toronto, ON, Canada; [4]Psychology, Washington Univ., St Louis, MO; [5]NIH, Bethesda, MD; [6]Neurol., Children's Hosp. of Pittsburgh, Pittsburgh, PA

Abstract: The recovery of perceptual functions that occurs following cortical damage can offer key insights into the nature and plasticity of brain organization. In this respect, studies of individuals' post-lobectomy/hemispherectomy offer a unique window into the nature and extent of cortical plasticity. First, in contrast with more common lesions, the extent of the damage in such patients can be extreme (i.e. an entire hemisphere in some cases) yet, at the same time, very well controlled - both cortical and subcortical structures of the remaining hemisphere are

typically intact. Second, the extent of the recovery is often disproportionate relative to the extent of the damage - many compromised functions are regained partly or even completely. Our present work uses fMRI to characterize the changes in topography and functional organization of extrastriate cortex and of visual field maps (VFMs) in children who have undergone surgical lobectomy or hemispherectomy of ventral cortex (compared with control participants who have undergone resections to other areas such as dorsal cortex). We uncover atypicalities in the selectivity of high-level visual cortex to common visual categories (face, object, and word) and show changes in this reorganization over the course of time post-surgery. Plasticity in earlier parts of visual cortex appears more limited and retinotopic organization in the affected hemisphere is either absent or largely abnormal. Overall, the current results suggest that extensive removal of visual cortex may lead to atypical selectivity for common visual categories but has limited effect on plasticity of early visual cortex.

Disclosures: **M. Behrmann:** None. **T. Liu:** None. **A. Nestor:** None. **K. Kay:** None. **M. Vida:** None. **J.A. Pyles:** None. **X. Zhang:** None. **C. Patterson:** None.

Poster

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Program#/Poster#: 789.12/M27

Topic: D.04. Vision

Support: NEI Grant F32EY022863

Title: Exploring the representational structure in visual object-responsive cortex

Authors: ***T. A. KONKLE**[1], A. CARAMAZZA[2];
[1]Psychology Dept, [2]Psychology Dept., Harvard Univ., Cambridge, MA

Abstract: The human visual system is built to efficiently extract and encode the structure of the natural world, transforming information from early sensory formats into increasingly abstract representations of its content that support our behavioral capacities. What are the different levels of representation from “low” to “high” level properties? To explore a broad space of possibilities, we considered properties that reflect how we interact with objects (action), where they are found (context), what they are for (function), how big they are (real-world size), and what they look like (object gist). Estimates for these feature spaces were obtained for a set of 200 inanimate objects, using either behavioral rating experiments or image-based measures that capture global shape structure (Oliva & Torralba, 2001). Using fMRI, we obtained neural

response patterns for 72 of these items in 11 participants. To analyze the structure in the neural responses, we used a feature-modeling approach (Mitchell et al., 2008; Huth et al., 2012), which fits a tuning model for each voxel along a set of feature dimensions (e.g. object gist features, action features). In areas V1, V2, and V3, the responses were well-fit by the object gist model (mean r2=0.54) and performance in a leave-two-out classification procedure was near perfect (96% SEM=1%). In contrast, the higher level feature spaces were not significantly above chance prediction in this cortex. In object-responsive cortex beyond early visual areas, the object gist model also outperformed the more abstract feature spaces (83% SEM=3%). However, feature spaces of action, context, function, and real-world size all were also able to classify objects above chance (61%-68%). These models fit best along more anterior regions of object-responsive cortex, extending along PHC, TOS, and IPS. Thus, while these abstract properties of objects capture some of the structure in neural object responses, the results indicate that visually-responsive object cortex most strongly represents global form properties.

Disclosures: T.A. Konkle: None. **A. Caramazza:** None.

Poster

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Topic: D.04. Vision

Support: NINDS R01 NS078396

NSF BCS1358907

Title: Spatial and temporal dynamics of face processing in the human ventral temporal cortex

Authors: *V. RANGARAJAN[1], B. L. FOSTER[2], S. GATTAS[1], J. PARVIZI[1];
[1]Neurol. (SHICEP), [2]Psychology, Stanford Univ., Stanford, CA

Abstract: Functional neuroimaging studies have revealed regions within the lateral and ventral temporal cortex that exhibit category specific neuronal responses to visual stimuli such as faces, objects, and places. These category responses display a consistent spatial organization with respect to well-established anatomical landmarks such as the Superior Temporal Sulcus, Fusiform Gyrus and mid-Fusiform Sulcus. Though several studies have mapped the spatial organization of face responses, the slow temporal dynamics of fMRI have provided limited temporal details of such activations. Moreover, few studies have explored sub-category level

visual activations (e.g., human versus mammal faces) in these regions. In the current study, we utilized electrocorticography (ECoG) data from 6 subjects implanted with subdural electrodes during two tasks. Task 1 contained images of human faces, places, English words, Spanish words, numerals, foreign numerals, corporate logos, and false fonts; In Task 2, subjects saw faces or bodies without heads (human, mammal, bird, fish), objects, places, and limbs. In both tasks, subjects were instructed to press 1 when a red target appeared. Leveraging the high spatial and temporal resolution of ECoG, we analyzed High Frequency Broadband (HFB: 70-150 Hz) power changes across all channels. In concordance with our previous work (Rangarajan et al., 2014), several face-selective FG electrodes were identified bilaterally using the Task 1 data. Data from Task 2 were used to explore the temporal dynamics of activity in these (face-selective) electrodes of interest and their neighboring sites to determine if the onsets and peaks of their activations revealed novel information about the temporal evolution of face processing. Our analysis revealed that electrodes of interest (identified from task 1) showed both larger magnitude and earlier HFB response onsets (~110 ms +/- 0.19) to faces than their immediate neighbors, supporting their focal selectively. Additionally, when several face-selective segregated electrode clusters were identified, many showed near simultaneous face response onsets, rather than a hierarchical (posterior to anterior) temporal organization. Lastly, within face-selective areas, the onset of responses to sub-categories of faces was earliest for human faces compared to animal, bird, or fish faces by 15 +/- 0.22 ms. Altogether, our findings provide electrophysiological evidence for a temporal dissociation between face-selective and neighboring sites in processing face stimuli and in prioritizing human versus other sub-categories of faces in face-selective regions.

Disclosures: **V. Rangarajan:** None. **B.L. Foster:** None. **S. Gattas:** None. **J. Parvizi:** None.

Poster

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the National Institute for Neurological Disorders and Stroke (R01 NS052585-01, 1R21NS072652-01, 1R01NS070963, R01NS083534)

Title: Beyond Brodmann: Quantifying the functional and microstructural heterogeneity of human high-level visual cortex

Authors: *K. S. WEINER[1], M. BARNETT[1], S. LORENZ[2], J. CASPERS[2], A. STIGLIANI[1], K. AMUNTS[2], K. ZILLES[2], B. FISCHL[3], K. GRILL-SPECTOR[1];
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Abstract: Human high-level visual cortex consists of functionally and microstructurally heterogeneous areas. Here, we compared and quantified the heterogeneity of functional and cytoarchitectonic regions in human ventral temporal cortex (VTC) using cortex based alignment (CBA) techniques. Functional magnetic resonance imaging (N=12; 2.4mm isotropic voxels; TR=2s) and a standard localizer experiment (Stigliani et al., 2014) enabled the identification of face- (pFus-faces/FFA-1 and mFus-faces/FFA-2), place- (CoS-places/PPA), and limb-selective (OTS-limbs/FBA) functional regions of interest (fROIs). Using an observer-independent cytoarchitectonic method (N=10 postmortem brains, 20 micron resolution) to determine transitions in cortical microstructure, we identified four areas (FG1, FG2, FG3, and FG4; Caspers et al., 2013; Lorenz et al., 2014). fROIs and cytoarchitectonic (cROIs) regions were registered to the FreeSurfer average brain using CBA (Fischl et al., 1999). We then generated maximum probability cROIs and quantified the proportion of each individual subject's fROIs within each cROI. Our results reveal three main findings. First, face- and place-selective regions are cytoarchitectonically dissociable. Nearly all face-selective regions are localized in FG2 and FG4 (90±8%, mean±std), while CoS-places was localized in FG3 (77±7%). Second, fusiform face-selective regions are also cytoarchitectonically dissociable: pFus-faces is located in FG2 while mFus-faces is located in FG4. Third, multiple fROIs can be located within a single cROI as both OTS-limbs (81±20%) and mFus-faces (84±14%) are within FG4. Together, our findings indicate that cytoarchitectonic structure may constrain functional differentiation both within a domain (e.g. between mFus- and pFus-faces) and across domains (e.g. between mFus-faces and CoS-places), but that cytoarchitectonic regions may also contain heterogeneous functions (e.g. both face- and limb-selective regions). These findings link the functional heterogeneity to the microstructural heterogeneity of high-level visual cortex for the first time. Additionally, the finding that a single cytoarchitectonic region is functionally heterogenous challenges classic views of cytoarchitectonic areas.

Disclosures: **K.S. Weiner:** None. **M. Barnett:** None. **S. Lorenz:** None. **J. Caspers:** None. **A. Stigliani:** None. **K. Amunts:** None. **K. Zilles:** None. **B. Fischl:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CorticoMetrics. **K. Grill-Spector:** None.

Poster

790. Color Vision

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 790.01/M30

Topic: D.04. Vision

Title: Motion-Induced color appearance shift

Authors: *S. HONG[1], M.-S. KANG[2];
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Abstract: Surrounding chromatic context modulates perception of color, which indicates that color appearance is not solely determined by spectral light reflected from a surface or an object. Here we present a novel and strong chromatic induction, in which color appearance of two identical objects, presented on a equiluminant equal-energy-spectrum (EES) 'white' background, shifted away from each other by setting one of the objects in motion. The direction of shift in color appearance of the stationary one is consistent with the one observed after prolonged adaptation to chromatic contrast, desaturation. On the other hand, color appearance of the moving one becomes more saturated. The shift in color appearance of the stationary dot is not due to local adaptation, because the appearance goes back to the baseline color after motion offset. Further, continuous flickering of multiple dots in the surrounding context is not potent enough to induce color shift of the stationary dot, indicating that motion-specific neural response rather than transient neural signal causes the appearance shift. We propose that the shift in color appearance of the stationary and the moving dots result from neural normalization of chromatic responses triggered by motion. This novel color induction by motion demonstrates a tight coupling between color and motion processing.

Disclosures: **S. Hong:** None. **M. Kang:** None.

Poster

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Support: NEI EY021575 (Y.X.)

NEI EY007556 (Q.Z.)

NEI EY013312 (Q.Z.)

SUNY-RF-BNE

Research to Prevent Blindness, Inc.

Title: Neural locus of simultaneous color contrast

Authors: *A. KHACHATRYAN[1], P. FUNG[1], C. LE'PRE[1], R. BACHY[2], Q. ZAIDI[2], Y. XIAO[1];
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Abstract: Simultaneous color contrast is a classical contextual effect that has been extensively studied using psychophysics and modeling, but its neural locus remains uncertain. To address this question, we have recorded neuronal activity from macaque extra-striate cortex, using a psychophysical method that isolates lateral interactions from adaptation. Imaging of intrinsic optical signals was used to visualize color-preferring modules in areas V2 and V4, where hue maps were found in previous studies. Neuronal activities in and near these modules were then recorded with multi-channel electrode arrays. Two sets of visual stimuli were used. The first set comprised full-screen (40x30 degrees) modulations along cardinal axes in the DKL color space that correspond to color preferences of different subcortical channels. The second set was identical to the first one except that the central region remained static at the mid-gray. The static central region (2-8 degrees) fully covered the receptive fields of the recorded neurons. Perceptually, the physical modulation of color in the surround induced complementary colors in the central region, i.e. an opposite-phase modulation of reduced contrast was seen where no physical modulation was present. A critical signature for the neural locus of simultaneous color contrast is that cells should exhibit similar behavior, i.e. their maximal response to full-screen or surround modulation occur at opposite phases. Many cells in or near the color-preferring modules in V2 and V4 responded to full-screen modulation of color at the temporal frequency of the stimuli. This finding suggests an important role of color-preferring modules in encoding spatially uniform color, given that previous studies with random penetrations in V2 and V4 found fewer cells that responded to uniform color. While the vast majority of such cells in V2

responded maximally to similar temporal phases of the full-screen and surround modulations, a significant portion of them in V4 responded best to opposite phases of full-screen and surround modulations. These results suggest that simultaneous color contrast emerges in area V4 in functional compartments that are involved in color perception, which is consistent with previous findings that V4 plays an important role in various forms of contextual effect on color.

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Poster

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Topic: D.04. Vision

Support: NIH R01 EY023322

NSF 1353571

Title: The dynamics of color processing in humans measured with MEG

Authors: ***K. L. HERMANN**[1,2], D. PANTAZIS[2], B. R. CONWAY[1,2];
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Abstract: At what point after a stimulus arrives at the eye is its color decoded by the brain? To address this question, we applied a decoding analysis to determine the time at which color information can be read out from a magnetoencephalography (MEG) signal. We presented two types of stimuli: color stimuli, and images of human faces and bodies. The color stimuli were square patches (6.2° across), of four hues at four luminances (i.e. 16 stimuli), presented at the fovea surrounded by a neutral gray. The colors were defined by a cone-opponent color space, had matched saturation, and were +/-30% or +/-60% luminance contrast. Each stimulus appeared 50 times in random order. Data were sampled at 1 kHz using a 306-channel Elekta Neuromag Triux, and pre-processed with Maxfilter software (Elekta) and band-pass filters (Brainstorm software; Tadel et al., 2011). Decoding analyses were done using the Neural Decoding Toolbox (Meyers, 2013) with a maximum correlation coefficient classifier. We did 50 decoding iterations, with 4 cross-validation splits, averaged trials in sets of 10, and used the 25 most selective channels at each time point. On average (in N=3), the onset latency for decoding faces versus

bodies was 91-96 ms. By comparison, we were able to determine which color (of 16 presented) a subject was shown as early as 78-83 ms after stimulus onset ($p < 0.005$, permutation test). To test whether luminance or hue information alone could drive decoding performance, we created two models. In Model 1, for each color, we assigned the correct luminance label with probability equal to the accuracy observed on a separate luminance decoding problem, and chose the hue label at chance. In Model 2, we assigned hue labels with probability equal to accuracy observed in a hue decoding problem, and luminance labels, at chance. We compared the relative magnitudes of the observed color decoding accuracy and the model predictions at the time of peak decoding; neither model accounted for the accuracy observed ($p < 0.001$ for both comparisons, by permutation test), suggesting that the observed color decoding depends upon neural sensitivity to both hue and luminance. But at what point in the visual system? Representational similarity analyses show that MEG onset latencies of 50-80 ms correspond to V1 activity (measured with fMRI), while those of 80-200 ms correspond to IT activity (Cichy et al., 2014). Isik et al. (2014) decoded the identity of object images at 60 ms, and identity invariant to changes in size and position at 125 and 150 ms. Taken together, our results on body/face decoding and color decoding suggest that the colors presented here are decoded relatively late in the visual-processing hierarchy, perhaps V4 or IT.

Disclosures: **K.L. Hermann:** None. **D. Pantazis:** None. **B.R. Conway:** None.

Poster

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Support: NIH R01 EY023322

NSF 1353571

Title: Color perception can be multistable as revealed by #TheDress

Authors: ***B. R. CONWAY**[1,2], K. L. HERMANN[1,2], R. LAFER-SOUSA[2];
[1]Neurosci., Wellesley Col., Wellesley, MA; [2]Brain and Cognitive Sci., MIT, Cambridge, MA

Abstract: To guide behavior, the brain must resolve ambiguity of sense data. Ambiguous shape information is typically resolved into two or three stable states. At any instant, the Necker cube is seen as popping out, receding away, or rarely as a hatch-work on a plane. How does the visual

system resolve color ambiguity? Although people might disagree about the exact color of a test (teal, blue, or green?), it has been widely assumed that most subjects would match the test to essentially the same color target, suggesting the disagreement is more about variability in language than perceptual mechanisms. We revisited this question by quantifying the perception of 'the dress' photograph. The colors of individual pixels when viewed in isolation are blue or brown, colors associated with natural illuminants, but popular accounts suggest the dress appears white/gold or blue/black. The phenomenon was an internet sensation because it seems to contradict popular belief, suggesting that color is, in fact, subject to discrete stable percepts (multistability). But there is a less exciting alternative: that the observed categorical responses arose because the social-media question was framed as a two-alternative forced choice. We used two experiments to test these alternatives. We surveyed 1348 subjects using Mechanical Turk and 53 subjects in-lab. First, we asked subjects to complete the sentence: "this is a ___and___dress". Most subjects reported white/gold or blue/black, but some said blue/brown. Second, we performed a language-free color-matching experiment in which we asked subjects to identify from a complete color gamut the two components of the dress. Each color match was defined by three coordinates (L, u, v). We used principle component analysis to define a vector through the cloud of data points (separate analysis for the two dress' components), and plotted for each subject the weight of the first PC for the "blue" pixels against that for the "brown" pixels. The plot shows three peaks, which correspond to the color-matches of the three sub-populations (W/G, B/K, B/B) identified in experiment 1. These results document one of the most compelling examples of striking individual differences in color perception, and show that the brain resolves ambiguity in 'the dress' into one of three stable states, not unlike how the brain handles ambiguous shape. But the "stickiness" of these states seems to be different for 'the dress' compared to the Necker cube. Although we found that the colors of the dress switch for some people (~11%), it appears that many people are incapable of switching their perception of the dress (unlike the Necker cube), and for those who do switch, the dynamics are slower.

Disclosures: B.R. Conway: None. **K.L. Hermann:** None. **R. Lafer-Sousa:** None.

Poster

790. Color Vision

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Program#/Poster#: 790.05/M34

Topic: D.04. Vision

Title: Effect of the mode of color appearance upon amplitude of steady-state visual evoked potential

Authors: *H. HIROSE[1,2], Y. KOIKE[2];
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Abstract: Several studies have been making clear that amplitude of steady-state visual evoked potential (SSVEP) varies in relation to physical aspects (e.g. brightness, hue and saturation) of flickering visual stimulus. However, there were little studies that revealed association between SSVEP amplitude and psychological aspects. This study aimed to elucidate the association between SSVEP amplitude and the mode of color appearance that is a psychological phenomenon. We investigated about SSVEP amplitude changes under two kinds of the mode of color appearance (aperture and surface color mode) condition. In experiment 1, we instructed subjects to gaze into 8 different flickering visual stimuli for 5 seconds under the conditions. Each stimulus was consisted of achromatic square and chromatic square that was colored with red, orange, yellow, yellow-green, green, blue-green, blue or purple. Their colors were selected from a Derrington-Krauskopf-Lennie (DKL) color space and were the same luminance (approximately 40 cd/m2). Flickering frequency of them was 12 Hz. Apparent size was 10 degrees. In the aperture and the surface color mode condition, background color was achromatic and has a luminance of approximately 0 cd/m2 and 40 cd/m2, respectively. These stimuli were presented one at a time on the center of a LCD screen. Electroencephalograms (EEGs) were measured at 8 loci (POZ, 3, 4, 7, 8 and OZ, 1 ,2) on the back of the head over the visual area of brain. Power spectral densities were calculated from the measured EEGs by using a frequency domain analysis. We focused on amplitude changes of fundamental component (F1) and second harmonic component (F2) of SSVEP. From the experiment 1, SSVEP amplitude changes related to the color of the flickering visual stimuli were observed in each condition. Furthermore, the SSVEP amplitude changes related to the mode of color appearance were also detected. These changes occurred in both the F1 and the F2. The SSVEP amplitudes obtained in the surface color mode condition had a tendency to be larger than those in the aperture. In experiment 2, we instructed the subjects to rank the flickering visual stimuli according to his/her flickering perception under the conditions. The subjects orally answered the rank in the descending order. These stimuli were simultaneously presented on the LCD screen. The other presentation methods were the same as the experiment 1. From the experiment 1 and 2, we found a positive correlation between the amplitude changes of the F2 and the rank of the stimuli in the aperture color mode condition. These results suggested that both physical and psychological aspects of flickering visual stimulus could influence SSVEP amplitude.

Disclosures: H. Hirose: None. **Y. Koike:** None.

Poster

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Support: CDMRP Grant MR130266

Title: Differential cerebral sources of human color responses

Authors: *C. W. TYLER[1], L. LIKOVA[2];
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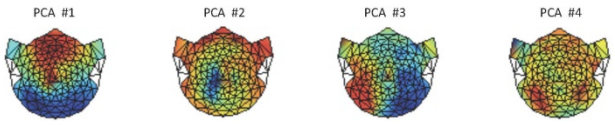
Abstract: Introduction. Color responses have been extensively studied in terms of their temporal and spatial properties, but little work has been done to identify their sources within the brain and the time courses of the color responses for the respective sources. Methods. Electrical responses to uniform 180 deg color fields were recorded on a 128-electrode whole-head EEG recording system (EGI). Color fields of 465 nm, 540 nm and 605 nm were modulated sinusoidally at 5 Hz and the response waveforms recorded for 60 s. The waveforms were averaged to the 200 ms cycle timebase and filtered 60 Hz pick-up and blink artifacts. A spatiotemporal component analysis identified the scalp topography of the source activations for each stimulus color. Results. Temporal response components were identified with latencies from 40 ms to 170 ms after the positive-going zero-crossing of the sinusoidal waveform. These components had distinctive scalp topographies, including a ventral occipital band, a focal vertex peak, a lateralized occipital dipolar response, and double-peaked occipital response. Component analysis of the response time courses showed classic bimodal, rectifying unimodal and local spike-like waveforms. Conclusions. This first study of the differential scalp topography of full-field color responses across the spectrum indicates markedly different source distributions and response timings for the respective color channels. Part of the differences in topography can be attributed to the differential foveal-to-peripheral weighting of the S-cones relative to the L- and M-cones across the retina, and to the complementary distribution of the rods (which were shown contribute to the cortical responses even at relatively high luminance levels). The shortest-latency responses are shorter than the known latency of any cortical responses, and may represent the first report of EEG response from the lateral geniculate nucleus.



Disclosures: **C.W. Tyler:** None. **L. Likova:** None.

Poster

790. Color Vision

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 790.07/M36

Topic: D.04. Vision

Title: Determinants of qualia of a profoundly ambiguous stimulus in the domain of color vision

Authors: *P. WALLISCH;
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Abstract: Subjective perception of the environment is highly idiosyncratic. This is not surprising, as the interpretation of the physical world is fundamentally underdetermined by the information available to the brain. Although all stimulus displays are inherently ambiguous, "bistable stimuli" - stimuli with two stable (with varying time constants) and radically different interpretations are usually used to study the way in which the brain makes inferences about the outside world. Such stimuli have been known in the domains of object and motion vision for well over a century, but were thought not to exist in the domain of color vision until February 2015. Here, we report on the subjective color perception of the picture of a dress that is typically perceived either as white and gold or as black and blue. We recruited 7917 participants online, mostly via media and social media. Data was collected online, via a 20 question survey hosted on Surveymonkey.com. We asked questions about the subjective perception of the dress, such as whether the percept switched after the first exposure as well as questions about lifestyle and demographics, such as chronotype (i.e. whether participants are most active during daytime or whether their circadian rhythms are phase-shifted), age, time spent outside or time spent in front of screens. 61% of respondents saw the dress as white and gold during the first exposure and most participants (94%) report that they were unaware of the true color of the dress at that point. This percept was modulated by factors such as circadian type or whether participants believed the dress to be in a shadow when the picture was taken, with a modulation range between 5 and 15 percent. Effect sizes like those for gender, age or favorite color were small (modulation ranges on the order of 1-3%), but nevertheless significant as the large sample sizes conveyed strong power. We conclude that our results support the interpretation that different priors for luminance and fabric as well as differing beliefs about illumination can account for most of the reported differences in subjective experience of dress color while demographic factors do not.

Disclosures: P. Wallisch: None.

Poster

790. Color Vision

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Support: KAKENHI 25135718

Title: Color and luminance selectivity of neurons in the monkey inferior temporal cortex using high-dynamic-range display

Authors: *K. KOIDA;
EIIRIS, Toyohashi Univ. of Technol., Toyohashi Aichi, Japan

Abstract: Color is a manipulatable attribute independent to the shape and luminance. Some neurophysiological and psychological studies support the independence of color signals; however, those examinations were limited in stimulus range due to the display gamut. Here, I examined color selective response and luminance dependency of the neuron in the anterior inferior temporal cortex of the macaque monkey using a custom-made, high-dynamic-range display. Stimuli were an equiluminant uniform surface with its color systematically distributed from the RGB gamut of the display. Luminance varied from 1 to 500 cd/m2. Single unit recordings were made of the awake monkey and stimuli were presented on the center of the screen while the animal was fixating. Besides the known type of cells showing invariant color selectivity across the 1:500 luminance range, I found that color-selective cells showed novel luminance selectivity, which prefers specific luminance. Those cells showed similar color selectivity to the isochromatic colored object which has luminance shades. This color selectivity indicates that both color and luminance were jointly coded and might form the invariant color cognition of colored objects.

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Poster

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Title: Cortical representation for the categorical color perception in infants investigated by near-infrared spectroscopy

Authors: ***J. YANG**[1], S. KANAZAWA[2], M. K. YAMAGUCHI[1], I. KURIKI[3];
[1]Chuo Univ., Tokyo, Japan; [2]Japan Women's Univ., Kawasaki, Japan; [3]Res. Inst. of Electrical Communication, Tohoku Univ., Sendai, Japan

Abstract: Perceptual color is continuous, however we tend to classify colors into a handful number of categories. Color categories are closely related to language, and are known to be common among most developed languages. Several behavioral studies have reported that infants hold categorical color perception (e.g. Bornstein, Kessen, & Weiskopf, 1976; Franklin & Davies, 2004). However, it is controversial whether color categories are inherent to the structure of the visual system. In the present study, we measured brain activity changes in prelinguistic infants (5- to 7-months old) in relation to categorical color differences using near-infrared spectroscopy (NIRS). Two types of visual stimuli were used: color alternations (1Hz) between green and blue or between two shades of green for between- and within-category conditions, respectively. Color differences were equated in CIE Lab space for both stimuli. Channels around the T5 and T6 in the International 10-20 system showed selective increase in oxy-Hb for the between-category condition. However, such selectivity was not observed in occipital region. This implies that different color categories are represented differently in the bilateral temporal regions in infants of 5-7 months. The 12 channels in each hemisphere were further classified into anterior, posterior, dorsal, and ventral groups. The grouped-channel analysis showed a significant activity in the posterior part in both hemispheres. The T5/T6 channels correspond near the border of middle temporal gyrus and fusiform gyrus in each hemisphere, and, in adults, the Wernicke's area resides in the anterior part of this junction in the left hemisphere. However, the adults' NIRS data did not show significant laterality. Also, lingual process in the Wernicke's area is known to start after 13-14 months from birth. Our results suggest that categorical color perception could be based mainly on visual, non-lingual, processing.

Disclosures: **J. Yang:** None. **S. Kanazawa:** None. **M.K. Yamaguchi:** None. **I. Kuriki:** None.

Poster

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Topic: D.04. Vision

Support: NIH Grant EY016155

University of Louisville

Title: Receptive field properties of neurons in primary visual cortex (V1) of normal and red light reared tree shrews

Authors: W. DANG[1], P. S. MAIRE[1], *H. M. PETRY[2];
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Abstract: Tree shrews (Tupaia) possess dichromatic color vision based on short-wave-sensitive (SWS) and long-wave-sensitive (LWS) cones. Deep red-light-rearing (RLR) selectively deprives SWS cones, and produces a differential stimulation of color and luminance pathways. Our behavioral studies showed that even after many months of subsequent housing in normal white light, RLR shrews display poorer color discrimination (Petry & Kelly 1991) coupled with enhanced visual motion sensitivity at high temporal frequencies (Callahan & Petry 1995). Retinal ganglion cells (RGCs) of RLR shrews also are tuned to higher temporal frequencies (Lu & Petry, 2002) indicating an initial retinal locus of this effect. Two-photon imaging showed this enhancement to be present in neurons in layers II/III of V1 in RLR shrews (Van Hooser et al., 2014). The present study assessed receptive field (RF) properties of single neurons in layer IV, the primary target of geniculate projections to V1. RLR shrews were reared from birth to 8-wks of age in deep red light (Kodak 1A tungsten illumination), then housed in normal white light until recording. Extracellular responses (obtained with metal microelectrodes) from single V1 neurons in adult normal and RLR shrews were used to measure temporal tuning curves and spatiotemporal receptive fields (STRF). Stimuli were drifting achromatic sine-wave gratings and sparse noise, respectively. Band pass, but not low pass, cells in RLR V1 showed stronger responses to higher temporal frequency stimuli. This finding strengthens our evidence for an enhancement of temporal vision (paired with a deficit in color vision) in RLR shrews that can be perceived and used in their behavior. This result, taken with our imaging data (Van Hooser et al., 2014) indicates that striate cortex is capable of processing higher temporal frequencies than those commonly recorded in normally-reared animals and suggests that temporal filtering mechanisms in cortex can be mediated by other inputs (e.g., color pathways). A competitive interaction (likely at earlier levels of processing) during post-natal development is indicated. A variety of STRF structures were found in both groups. Most cells had a biphasic temporal response, with spatially overlapped ON- and OFF-centers. About 2/3 of those cells had single ON and OFF sub-fields, thus could be fitted with two Gaussians, while the other 1/3 had spatially discontinuous ON or OFF regions. While most cells revealed space-time separable RFs, a very small proportion were space-time inseparable. The preferred frequencies of cells were much lower than the linear prediction of their STRFs, suggesting a nonlinear mechanism in temporal processing.

Disclosures: W. Dang: None. **P.S. Maire:** None. **H.M. Petry:** None.

Poster

790. Color Vision

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Topic: D.04. Vision

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NIH Grant EY018849

Title: Linear and nonlinear cone signal combination in macaque V1

Authors: *J. P. WELLER, G. D. HORWITZ;
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Abstract: In the Old World primate retina, signals from the L- and M-cones combine synergistically and antagonistically to form the basis of luminance and chromatic vision. How these cone signals are represented in the primary visual cortex (V1), however, remains poorly understood. Early investigations found that most V1 neurons represent cone signals as a weighted sum, but a more recent study found that approximately half of V1 neurons combine cone signals nonlinearly (Horwitz and Hass, 2012). This nonlinearity may derive in part or entirely from the stimulus they used - a drifting Gabor patch that encroached on the extraclassical surround - or even from interactions within the classical receptive field (RF), itself. If so, we expect small, brief stimuli to elicit responses with a greater degree of linearity than observed with larger, more complex stimuli. We tested this hypothesis by measuring the responses of V1 neurons to punctate flashes targeted to spatially distinct RF subunits. A rhesus macaque fixated a central spot on a CRT monitor. We probed each V1 neuron in a two-stage procedure. First, we used a spatiotemporal white noise stimulus to modulate L- and M-cones randomly. From the spike-triggered average stimulus, we identified individual subunits within the classical RF, then presented brief (200 ms) flashes to the selected subunits (n = 100). The flashes modulated L- and M-cones in varying ratios and degrees; the broad scope of tested modulations allows for an unbiased, model-free assessment of response tuning across the LM plane of color space. The results revealed that many V1 neurons (~60%) carry a weighted sum of L- and M-cone signals, and that, within this population, cone weights in are highly stereotyped, with luminance cells having equal L- and M-cone weights (i.e. 1:1), and chromatic cells having equal-and-opposite weights (i.e. 1:-1). Some of these neurons responded to a both polarities of modulation along the luminance or chromatic axes, but others to only a single polarity. Responses of neurons sensitive to both color and luminance (~40%) are poorly described as a

weighted sum of cone signals, but are still highly stereotyped, and can be described by a relatively simple nonlinear combination of signals from luminance and chromatic neurons. As shown previously, some neurons responded to all directions in the LM plane. Here, however, we report the novel result that some V1 neurons responded to all but a single direction in the LM plane (e.g., all but red), and still others to only two perpendicular directions (e.g. red and +luminance). These results reveal how V1 builds up a mutual chromatic and luminance sensitivity to form the foundation for downstream color invariance.

Disclosures: J.P. Weller: None. **G.D. Horwitz:** None.

Poster

790. Color Vision

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Topic: D.04. Vision

Title: Non-linear visual cortical activity linked to human color perception

Authors: *R. M. SHAPLEY[1], V. NUNEZ[2], P. SCHUETTE[2], A. HANINEVA[2], A. AMIR[2], C. VELOZ[2], S. WHITTICK[2], J. GORDON[2];
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Abstract: Neurons in primary visual cortex (V1) have characteristics that link them to the processing of fundamental aspects of color perception. We examined this linkage quantitatively in humans by using hue and saturation scaling as a measure of perceived color and the chromatic visual evoked potential (cVEP) as a measure of neural activity. Isoluminant appearance-disappearance checkerboards or isolated-check patterns were square-wave modulated (0.5s on, 1.5s off) from gray to color and back to gray. The patterns had chromatic excitation purities ranging from 0.03 to 0.53. The square stimulus field was 10° across and the checks were 18.75' or 37.5' of arc. Luminance was 31.5 cd/m2. Human observers rated the stimuli for apparent color saturation. Apparent saturation was proportional to excitation purity. In the same observers we recorded cVEPs with a 64-channel BioSemi system. Responses were signal-averaged (30 repeats) and Fourier-transformed. The largest cVEPs were concentrated at electrodes at or around Oz, pointing to V1 as the major source of these responses. Previously the work of others indicated that the cVEP is driven by neurons in V1. Unlike the perceptual scaling results, cVEP peak amplitude grew rapidly with purity and then hit a ceiling response at relatively low purities. cVEP waveform was non-linear; it became faster with increasing excitation purity. The non-linear characteristics of the EEG response are indicative of cortical processing since we know

that the Parvocellular LGN input to the cortex is highly linear. The non-linear change in cVEP waveform produced a phase-advance with increasing excitation purity in most Fourier components of the response. Harmonic analysis of the cVEP also revealed that Fourier components of the response in the 6-20 Hz range were proportional to excitation purity like the perception while lower frequency components hit an amplitude ceiling. Our results show that there is a very strong correlation between measures of color perception and higher frequency response components of the cVEP of early visual cortex.

Disclosures: R.M. Shapley: None. **V. Nunez:** None. **P. Schuette:** None. **A. Hanineva:** None. **A. Amir:** None. **C. Veloz:** None. **S. Whittick:** None. **J. Gordon:** None.

Poster

790. Color Vision

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: D.04. Vision

Support: PNWU seed grant

Title: A case of enhanced color vision

Authors: *R. SORRELLS;
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Abstract: Current medicinal philosophy emphasizes the whole person, yet our case reports are often about a collection of symptoms, or a disease. The current case study is about a whole person and the connection between his brain and mind. Born red-green color blind, this individual fell on his head in January of 2014 and woke up to a splendid world of color. Functional MRI indicates that his cortical visual and color areas are responding to color stimulation, most noticeably when he named the color he viewed silently to himself. In other words, the signal was strongest when he viewed and thought about the color name simultaneously. In behavioral testing using color strips and environmental stimuli, the individual has no problems picking out colors, making subtle distinctions between red and green, and more importantly, he has a strong emotional reaction to the colors, for example, when he found a yellow streak of hair in his wife's long platinum locks. However, he continues to fail the Snelling tests, due in part to a Horner's syndrome and severe stigmatism, suggesting that this standard test for color blindness is confounded with visual acuity. It is well known that context, for example form and shape, plays an important role in the perception of color, and there is a large interplay

between color knowledge (what the person perceives) and object color knowledge (what color the object is supposed to be). This suggests that perhaps the patient is using knowledge from what others have told him, along with the extra attention to the new colors, and this has enhanced his perception.

Disclosures: R. Sorrells: None.

Poster

790. Color Vision

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Topic: D.04. Vision

Support: NIH Grant EY021575

Research to Prevent Blindness, Inc.

Title: Spatial clustering of color-selective neurons in the striate cortex of macaque monkeys

Authors: A. KHACHATRYAN[1], P. FUNG[1], M. CRUMILLER[2], *Y. XIAO[1]; [1]Ophthalmology, SUNY Downstate Med. Ctr., Brooklyn, NY; [2]Lab. of Biophysics, The Rockefeller Univ., New York, NY

Abstract: Previous imaging studies have found hue maps in some visual areas of primates, including the striate cortex (V1). These studies suggest that these visual areas contain functional compartments where neurons are spatially organized according to their color preferences. To test this hypothesis, we have recorded single-unit activity from V1 of macaque monkeys and characterized each unit's cone inputs. Neuronal activity was recorded from anesthetized and paralyzed monkeys using 64- or 54-channel electrodes that spanned different columns or layers. High-quality spike sorting was achieved by an advanced algorithm that utilizes signals recorded from all channels (Swindale&Spacek, 2014). To determine cone contributions to each unit's receptive field (RF), we used Hartley stimuli that comprised cone-isolating gratings of various orientations, spatial frequencies and phases. RFs were reconstructed by reverse correlation. In agreement with previous studies, we found two types of RFs that received opponent L- and M-cone inputs. A double opponent (DO) RF had two main sub-regions that had opposite cone opponency (L+M- vs. L-M+). A single opponent (SO) RF had the same cone opponency across its receptive field. The sub-regions of the DO RFs were more elongated than the SO RFs, suggesting that the former were more selective for orientation than the latter. The SO RFs of

nearby units tend to have the same cone opponency, suggesting spatial clustering of SO neurons according to their color preferences. In contrast, there was equal chance for the DO RFs of nearby units to have the same or opposite cone opponency in each sub-region, suggesting that the DO neurons were not clustered according to their color selectivity for surface borders. Instead, the DO neurons were clustered according to their orientation preferences. Hue maps in V1 respond well to spatially uniform colors (Xiao et al., 2007), suggesting a major contribution from the SO neurons to their activity. Our result therefore supports the existence of hue maps in V1 where neurons are spatially clustered according to their color preferences. The SO and DO neurons may encode color information located at the interior and border of a surface, respectively. Their difference in spatial clustering points to different strategies for downstream areas to decode color information from these two populations.

Disclosures: **A. Khachatryan:** None. **P. Fung:** None. **M. Crumiller:** None. **Y. Xiao:** None.

Poster

791. Visual Behavior in Different Species

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Program#/Poster#: 791.01/M44

Topic: D.04. Vision

Support: AGIR (Alpes Grenoble Inovation Recherche), Univ. Grenoble Alpes

Title: Aging effects on the luminance contrast response in Humans

Authors: ***E. BELLOT**[1], E. MORO[2], K. KNOBLAUCH[3], V. COIZET[1], M. DOJAT[1];
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Abstract: Luminance contrast is a fundamental visual cue. Testing contrast response is of interest with respect to alterations in aging or in the progression of diseases, such as glaucoma and Parkinson's disease. Luminance contrast response functions were assessed in two ways. First, using high-resolution 3T-fMRI we explored for subjects with normal or corrected to normal vision and varying age (Young: n=10, 26±3Yo; Middle age: n=10, 47±4Yo; Aging: n=10, 65±3Yo), the luminance contrast response of three regions of interest (ROIs), located along the visual pathway and anatomically defined in each individual: i) the Superior Colliculus (SC), ii) the Lateral Geniculate Nucleus (LGN) and iii) the primary visual area V1. We used achromatic checkerboards varying in luminance (1-9%), flashing at 4Hz and alternately

presented in each visual hemi-field. Second, we estimated the perceptual response to contrast by using Maximum Likelihood Difference Scaling (MLDS), a method based on paired-comparisons of stimulus intervals and a signal detection model allowing estimation of response scales by maximum likelihood. In this psychophysical study, each participant performed 3 sessions, each session consisting of a 5 min random presentation of 120 ordered triads of checkerboards, draw from a set of 10 luminance contrast levels logarithmically spaced. The observer had to choose whether the middle contrast was more similar to the lower or higher one. Our results firstly demonstrated that, in all explored ROIs, BOLD responses increased progressively with luminance contrast. This confirms and extends to the low contrast range of previously published data. Moreover, a progressive decrease of the BOLD amplitude with age was observed in V1 and the LGN (V1 and LGN: $p<.01$). These data are consistent with the results obtained with the psychophysical task, showing on the one hand a response that increases with luminance contrast, reaching an asymptote at 20% and, on the other hand, a difference related to age at low range contrasts and even in the higher range tested. In conclusion, our findings indicate that the luminance contrast response is affected during normal aging, as tested by our rapid psychophysical technique, and also reflected by a BOLD signal decreasing along the visual pathway. Understanding the mechanisms underlying these changes that occur in normal aging is essential both for understanding the normal aging process and for comparisons between healthy aging subjects and aging patients with age-related visual and/or cortical/subcortical disorders.

Disclosures: E. Bellot: None. **E. Moro:** None. **K. Knoblauch:** None. **V. Coizet:** None. **M. Dojat:** None.

Poster

791. Visual Behavior in Different Species

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Topic: D.04. Vision

Support: Kakenhi Grant in Aid

RIKEN-BSI Research Grant

Title: Fully automated training system for head-fixed mice

Authors: R. AOKI, R. NISHIYAMA, Y. GOYA, *A. BENUCCI;
RIKEN Brain Sci. Inst., Saitama, Japan

Abstract: Training rodents in behavioral tasks is becoming an increasingly critical technique in Systems Neuroscience. However, not all rodents are equally suitable for training. The taxon rodents belong to (Rodentia) comprises of >2000 species, with an astounding diversity not only in the general phenotype (e.g. 1000 fold in body size) but also in their propensity for behavioral training. A classic example is the one of rats and mice. While rats are fairly easy to handle and train and can even be taught to self-restrain (Scott et al., 2013), mice are much more difficult in these respects, especially with the head-fixed setups often required for imaging/optogenetic experiments. Here we present a fully automated, head-fixed system for the behavioral training of mice. Mice are implanted with a 6mm-diameter head chamber for head fixation and for optical access to the brain. They are housed in a modified cage. Custom-made software (the controller) gives access to an adjacent self-latching zone twice a day, 30 min each time. After a pre-training phase of ~1 week, water-restricted mice learn to voluntarily latch their head chamber in order to reach a water spout. The controller then presents visual stimuli on a monitor in front of the animal for training in standard visual-discrimination tasks. The animal's choice is read out via a choice ball (Sanders & Kepecs 2012). The controller records the animal's weight for automatic alerts in case of unhealthy weight drops. Webcams connected to call-in software (Skype®) allow for 24/7 remote video access. We used this setup to train mice (n=3) in two-alternative forced choice tasks in contrast and orientation discrimination, and used signal-detection theory to quantify the behavioral performance (Fründ et al., 2011). For contrast discrimination, we used three levels of contrast difficulties (33%, 66%, and 100%). Mice easily learned this task reaching 90% correct. For orientation discrimination, we progressively increased the difficulty up to five levels, with a minimum orientation difference of 18 deg. Also in this case, performance reached 80% correct. When discrimination difficulty was increased, the psychometric sensitivity and success rate did not change significantly, suggesting that the mouse learned to generalize the discrimination rule. We are currently scaling-up the setups to implement parallel training strategies within a wider range of sensory decision-making tasks. Overall, we believe this approach will be ideal for combining high-throughput behavioral training with optical imaging and optogenetic experiments.

Disclosures: **R. Aoki:** None. **R. Nishiyama:** None. **Y. Goya:** None. **A. Benucci:** None.

Poster

791. Visual Behavior in Different Species

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 791.03/M46

Topic: D.04. Vision

Title: The evaluation of visual temporal resolution in the behaving mouse

Authors: *J. MITA[1,2], S. YOKOTA[3], S. IKUTA[2], S. TAKIZAWA[2], Y. NOMURA[4,2], T. ARIMURA[2,4], A. AMANO[5], K. SHIMONOMURA[6], Y. SEYA[7], Y. TSUBO[7], C. KOIKE[2,4,8]; [1]Life Sci., Ritsumeikan Univ., Kusatsu-Shi, Japan; [2]Lab. for Systems Neurosci. and Developmental Biology, Grad. Sch. of Life Sci., [3]Res. Organization of Sci. and Technol., [4]Lab. for Systems Neurosci. and Developmental Biology, Col. of Pharmaceut. Sci., [5]Dept. of Bioinformatics, Col. of Life Sci., [6]Dept. of Robotics, Col. of Sci. and Engin., [7]Dept. of Human and Computer Intelligence, Col. of Information Sci. and Engin., Ritsumeikan Univ., Shiga, Japan; [8]PRESTO, Japan Sci. & Technol. Agency, Saitama, Japan

Abstract: Purpose: Critical fusion frequency(CFF), defined as the frequency at which a flickering light is indistinguishable from a steady one, is one of the useful measures to evaluate visual temporal resolution based on functional separation of ON and OFF pathways. Temporal resolution has been studied by electrophysiological approach such as flicker electroretinogram(ERG) and visual evoked potential(VEP). However, the CFF analysis based on behavioral performance has not been studied. Here we established a method to evaluate visual temporal resolution in the behaving mice. Methods: C57BL/6 mice were trained to performance a two-alternative forced choice task in which steady illumination(250Hz) and flickering illumination(4-20Hz) were presented on a green light emitting diode(green LED, 508nm) screen. Mice responded to steady illumination by making nose-poke toward the screen. Each mouse performed the 4-Hz condition first, and proceeded to the next temporal frequency condition by reaching a criterion of proportion correct responses(PCRs) higher than 80% over three consecutive sessions. In the analysis, we determined a frequency that mice could not discriminate steady stimulation from flickering stimulation(approximately 50-60 percentage of correct) as CFF Results: In the 4-Hz condition, PCRs increased with sessions, and all the mice could discriminate between steady illumination and flickering illumination. Dynamic image analysis revealed that mice responded with shorter walking distances over the trials in the later sessions. In the frequency conditions of 5-10 Hz, all the mice reached the criterion within fewer sessions than in the 4-Hz condition. Although there were relatively large individual differences in the PCR data, the results suggested that CFF in the behaving mice is approximately 15Hz. Conclusion: We established the method to evaluate temporal resolution of ON and OFF pathway-mediated vision in the behaving mice. This behavioral assay of mouse model could contribute to development of diagnosis of human retinal disease by applying genetically manipulated mice.

Disclosures: J. Mita: None. **S. Yokota:** None. **S. Ikuta:** None. **S. Takizawa:** None. **Y. Nomura:** None. **T. Arimura:** None. **A. Amano:** None. **K. Shimonomura:** None. **Y. Seya:** None. **Y. Tsubo:** None. **C. Koike:** None.

Poster

791. Visual Behavior in Different Species

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 791.04/M47

Topic: D.04. Vision

Title: Topological perception in behaving monkeys: I. Visual search

Authors: J. HUANG[1], Y. YANG[2], X. ZHAO[3], Q. ZHOU[3], H. ZHU[4], K. ZHOU[3], *W. ZHOU[4], Y. ZHOU[1];
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Abstract: Behavioral, neurophysiological and computational studies have revealed a general scheme of visual shape recognition, which starts from extracting local features followed by a feature binding process (Treisman and Gelade, 1980; Hubel and Wiesel, 1982; Marr, 1982). However, there is accumulated evidence arguing that human vision starts from extracting topological features (e.g., number of holes), which then facilitate processing local features (Chen, 1982, 2005). While the topological perception challenges the generality of the prevailing model of visual shape recognition, little is known about the underlying neural mechanisms. The primary goal of this study is to establish a non-human primate model of detecting presence of a hole in a visual object, a typical topological property. Monkeys were presented with a set of white visual stimuli in a black background and were trained to make a saccade to the odd-ball target. While white disk was used as the distractor in all conditions, the odd-ball target was different from the distractor in color (RED DISK vs. WHITE DISK), shape (WHITE SQUARE vs WHITE DISK), or topological property (WHITE RING vs. WHITE DISK). In the first experiment, we found that saccade latencies to the WHITE RING target were similar to that to the RED DISK target, but were shorter than that to the WHITE SQUARE target. Further control experiments showed that the short-latency detection of the WHITE RING target was not due to differences in local features, such as spatial frequency and luminance. In the second experiment, we examined how combinations of local features, color and topological features affect saccade latencies to the odd-ball target. We found that combination of color with shape or the topological property reduced saccade latencies to the odd-ball target. For example, using white disk as the distractor, saccade latencies to the RED SQUARE target were shorter than that to the RED DISK target or the WHITE SQUARE target; saccade latencies to the RED RING target were shorter than that to the WHITE RING target or the RED DISK target. To our surprise, we found that combination of local shape features and the topological feature exhibited significant interactions.

For example, using white disk as the distractor, we found that saccade latencies to the WHITE SQURE-shaped RING target were similar to that to the WHITE SQUARE target, which were longer than that to the WHITE RING target. In summary, these preliminary results established a non-human primate model of early detection of the topological property. Ongoing studies will further characterize this model to investigate the underlying neural mechanisms.

Disclosures: **J. Huang:** None. **Y. Yang:** None. **X. Zhao:** None. **Q. Zhou:** None. **H. Zhu:** None. **K. Zhou:** None. **W. Zhou:** None. **Y. Zhou:** None.

Poster

791. Visual Behavior in Different Species

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 791.05/M48

Topic: D.04. Vision

Support: Brain MINDS from MEXT Japan

Title: Low ability to discriminate faces in common marmosets

Authors: *K. NAKAMURA, M. MIWA, R. KOBA, C. YAMAGUCHI, A. TAKEMOTO; Primate Res. Institute, Kyoto Univ., Inuyama, Japan

Abstract: We investigated characteristics of visual discrimination in common marmosets (Callithrix jacchus). Five marmosets were trained in a visual delayed matching-to-sample task. In this task, they were required to touch a visual sample stimulus presented on a PC monitor. After a short delay period, two visual stimuli were presented. One was the sample stimulus and the other was a stimulus different from the sample. They were required to touch the sample stimulus to obtain a reward. We used four categories of visual stimulus; graphic patterns, photographs of food, photographs of a flower, and photographs of a marmoset face. We first trained the marmosets with graphic patterns. Thereafter, we introduced 3 categories of photograph. All of the five marmosets quickly reached a criterion under the food- and flower-conditions. However, they hardly reached the criterion under the marmoset face-condition. Apparently, they showed difficulty in discrimination of marmoset faces. Common marmosets live in families. Within a family group, the breeding male and female are dominant. For the other members, social rank is usually based on age. Low social demand for discrimination of conspecific's faces can account for this low discrimination ability of faces.

Disclosures: **K. Nakamura:** None. **M. Miwa:** None. **R. Koba:** None. **C. Yamaguchi:** None. **A. Takemoto:** None.

Poster

791. Visual Behavior in Different Species

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Topic: D.04. Vision

Support: NSF RTG DMS-1344962

NSF RTG DMS-0636358

Title: Is our sensing compressed?

Authors: ***G. KOVACIC**[1], V. BARRANCA[2], D. CAI[2];
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Abstract: Along the early stages of several sensory pathways, significant downstream reductions occur in the numbers of neurons transmitting stimuli. For example, in the retina, photoreceptors outnumber retinal ganglion cells by a factor of 100, and in the olfactory pathway, the olfactory receptors outnumber the mitral and tufted cells by about the same factor. To understand how much information is retained in such a reduction, we model it using an idealized neuronal network. Our model has two layers, receptors and sensory neurons immediately downstream, connected randomly and sparsely, with the receptors considerably outnumbering the sensory neurons. Our work reveals a mechanism for preserving information through bottlenecks in sensory pathways, related to the preservation of image quality using compressed-sensing type data acquisition. Through numerical simulations, we show that most information is retained when the convergence from the receptors to sensory neurons equals the ratio between the numbers of those two neuron types, and that information flow depends little on the connectivity architecture among the model sensory neurons. We find an optimal strength of the connections between the receptors and sensory neurons in the model. We find that the spike trains in the model network that retains most information exhibit the most variability, as represented by the maximal entropy, closest distance to gaussianity of their interspike-interval distribution, and least correlation times. In addition, the average neuronal membrane potential in such a network (roughly mimicking the local field potential) has the broadest power spectrum. Finally, we show that the more realistic version of the model, which samples the stimulus through localized

receptive fields rather than randomly as is common in engineering applications, retains at least 50% more information.

Disclosures: **G. Kovacic:** None. **V. Barranca:** None. **D. Cai:** None.

Poster

791. Visual Behavior in Different Species

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Topic: D.04. Vision

Support: NSC 101-2321-B-002-078

NSC 102-2321-B-002-059

MOST 103-2321-B-002-028

Title: The detection of contrast polarity of visual images in behaving rats

Authors: *C.-I. YEH[1,2,3], S.-H. WU[3];
[2]Psychology, Neurobio. and Cognitive Sci. Ctr., [1]Natl. Taiwan Univ., Taipei, Taiwan; [3]Grad. Inst. of Brain and Mind Sci., Natl. Taiwan Univ. Col. of Med., Taipei, Taiwan

Abstract: In several diurnal species including cat, macaque monkey and human subjects, many neurons in the primary visual cortex V1 have stronger responses to stimuli with negative contrast (black on gray) than with positive contrast (white on gray). The asymmetry in responses to different contrast polarities may explain why human subjects can detect negative contrast better and more easily than positive contrast. The black-over-white bias found in diurnal animals is ecologically plausible because it may help them to escape from predators that appear in a relatively brighter background. On the contrary, nocturnal animals such as rodents may need to develop a bias in detecting positive contrast. In accordance with this hypothesis, strong white-dominant responses were recently reported in rodent V1 with the voltage-sensitive dye (VSD) imaging technique (Polack & Contreras, 2012). Here we used a two-alternative forced choice task to test the contrast preference in behaving rodents (Long Evans). The rat started each trial in the central port of a three-arm device with a monitor in front of the animal. A bright or dark square against a gray background was then shown briefly on the left or right portion of the monitor. The animal was rewarded if the choice was correct (moving to the left or the right port where the stimulus was shown). We manipulated both the contrast (0%, 4%, 8%, 16%, 32%, 48%, 64%, 100%, either positive or negative in Weber contrast) and the mean luminance of the

screen (high: 50 cd/m2, low: 20 cd/m2). Surprisingly, preliminary results showed that the detection threshold tended to be lower for negative contrast than for positive contrast. The black-over-white bias is the largest at 100% contrast under the low luminance condition. The discrepancy between behavioral and neuronal results in rodents may be due to 1) the duration of the visual stimuli and 2) the difference in the mean luminance of the monitor. Overall, these behavioral results suggest that rodents, like other diurnal species, might be more sensitive to negative contrast than positive contrast.

Disclosures: **C. Yeh:** None. **S. Wu:** None.

Poster

791. Visual Behavior in Different Species

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 791.08/N3

Topic: D.04. Vision

Support: NIH R01-EY020958 (to WJM)

Title: Memory precision in a contrast estimation task

Authors: ***S. JACKSON**[1], W. J. MA[1,2];
[1]Ctr. for Neural Sci., [2]Dept. of Psychology, New York Univ., New York, NY

Abstract: By providing continuous, high-resolution measurements of memory contents, delayed-estimation tasks have elucidated the nature of visual short-term memory (VSTM), most notably for orientation and color [1]. Such features are relatively stable across time [2], presumably due to the topographic form of their neural representations. For intensity-coded features such as luminance contrast, however, VSTM might be less stable over time [2]. Unfortunately, VSTM for luminance contrast has been characterized predominantly using relatively coarse discrimination tasks. Here, we systematically examined VSTM for luminance contrast using delayed estimation. On each trial, a small circular disc (1° diameter) was briefly presented (200 ms) to observers either left or right of fixation (4° eccentricity). Luminance contrast of the disc was set to one of eight positive values, which were interleaved in randomly shuffled order across each block of trials. After a brief delay (1500 ms), a disc of random contrast was presented at the same location as the first. Observers adjusted the contrast of the second disc (through thirty-eight possible values) until it matched the memorized contrast of the first, by moving a computer mouse horizontally. Trials were separated by an ITI of 1500 ms. Data (n = 8) consisted of estimate probability distributions for each of the tested contrasts.

Distributions were clearly distinguishable from one another, on average showing only a small bias towards the mean presented contrast. As contrast increased, the distributions shifted accordingly, and inter-quartile range broadened in approximately Weber's law fashion. We fit the data using a probabilistic model of neural responses, assuming Poisson noise and maximum-likelihood readout. When realistic forms of the contrast response function were incorporated into the model (e.g., Naka-Rushton, power law), it provided good quantitative fits to the distributions, predicting neurally plausible gain parameter values (e.g., Naka-Rushton exponent of ~2). In summary, error distributions for luminance contrast have not previously been investigated using delayed estimation, and may provide rich information for testing theories of VSTM for contrast. We measured these distributions and successfully characterized their shapes using a probabilistic model of neural responses. Future work may investigate how the distributions change with delay time and set size manipulations. Refs: [1] Ma et al., Nat. Neurosci., 17: 347-356, 2014; [2] Magnussen & Greenlee, Psychol. Res., 62: 81-92, 1999.

Disclosures: **S. Jackson:** None. **W.J. Ma:** None.

Poster

791. Visual Behavior in Different Species

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 791.09/N4

Topic: D.04. Vision

Title: Dynamic allocation of visual resources under change of task

Authors: *P. LADDIS[1], S. GEPSHTEIN[2], T. ALBRIGHT[2];
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Abstract: We investigated how visual systems allocate their limited resources according to the demands of visual tasks. From Gabor's uncertainty relation it is expected that large receptive fields are more suitable for measuring stimulus frequency content ('identification') and small receptive fields are more suitable for measuring stimulus location ('localization') (Gepshtein et al., 2007). Visual systems would benefit from relying on small receptive fields for localization and on large receptive fields for identification. We tested whether human vision follows this strategy, i.e., whether the extent of spatial integration depends on visual task. In Experiment 1, we measured the spatial contrast sensitivity function (CSF) in identification and localization tasks using the same stimuli, under conditions of equal task difficulty. Sensitivity increased at low spatial frequencies and decreased at high frequencies in identification relative to localization, as if the sensitivity function shifted towards low frequencies, supporting the

prediction. In Experiment 2, we found that amplitude modulation sensitivity (Jamar et al, 1982) changed similarly. In Experiment 3, we observed that changing the task from localization to identification increased the critical area of spatial summation (Inui, 1981). Together, these results suggest that receptive field sizes are dynamically adjusted to meet demands of visual tasks.

Disclosures: **P. Laddis:** None. **S. Gepshtein:** None. **T. Albright:** None.

Poster

791. Visual Behavior in Different Species

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Topic: D.04. Vision

Support: DFG EXC 307

ERC Starting grant 281885 - PERCEPT

Title: Mice can use second-order stimulus cues to guide visual perception

Authors: Z. KHASTKHODAEI[1,2], O. JURJUT[1], S. KATZNER[1], *L. BUSSE[1];
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Abstract: In primates, visual processing along the ventral stream takes place in a hierarchy of areas, characterized by an increase in invariance to changes of low-level stimulus attributes. A simple form is “cue-invariance”, where neurons show similar preference when driven by first-order stimuli (defined by changes in luminance) or second-order stimuli (e.g., defined by changes in contrast). While mice have gained popularity a as model system for early visual processing, it is still unclear whether their vision relies on more than luminance cues. Here, we asked whether mice can generalize orientation discrimination in a cue-invariant way, potentially mediated by cue-invariant representations of orientation in visual cortex. To address this question, we used first-order, luminance-modulated gratings *(LGs)* and second-order, contrast-modulated gratings *(CGs)*. We created two types of *CGs*, which consisted of a sinusoidal envelope with a spatial frequency optimal for mouse visual cortex and a static 1/f noise carrier, that differed in the distribution of Fourier energy. The low-frequency type contained all noise energy < 0.12 cyc/deg, the high-frequency type > 0.12 cyc/deg. We first tested whether mice can generalize from a learned orientation-reward association with *LGs* to different types of untrained *CGs*. We used a classical conditioning task, in which mice learned to perform an orientation

discrimination task on *LGs*. After learning (AUROC = 0.77), we replaced the *LGs* by *CGs* (low-frequency type), and found that, despite overall lower performance (AUROC = 0.63), mice could readily generalize across the two types of stimuli. Performance better than chance could even be observed for high-frequency type *CGs*, which do not contain energy in the typical pass-band of mouse V1 neurons. We then performed extracellular recordings in areas V1 and LM, where we compared orientation tuning curves to *LGs* and *CGs*. We noticed that fewer neurons responded to *CGs* than to *LGs* (area V1, 86%; area LM, 63%; $p < 10^{-4}$). For those neurons with significant responses to both types of gratings, peak responses were weaker to *CGs* compared to *LGs* ($p = 0.005$). Furthermore, orientation selectivity was lower for *CGs* compared to LGs, and this reduction was particularly pronounced for area V1 ($p = 0.006$). Despite this generally reduced responsiveness and selectivity for *CGs*, preferred orientations in response to *CGs* and *LGs* were broadly similar ($p = 0.005$). We conclude that mice can, at least in a rudimentary form, use second-order stimulus cues to guide visual perception and that this ability might potentially be mediated by a cue-invariant representation in early visual areas.

Disclosures: **Z. Khastkhodaei:** None. **O. Jurjut:** None. **S. Katzner:** None. **L. Busse:** None.

Poster

792. Visual Processing: Learning, Memory, and Categorization

Location: Hall A

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Topic: D.04. Vision

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Title: Grouped icEEG evaluation of the temporal pole during visual naming of common and proper nouns

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Abstract: Selective conceptual deficits for unique entities (i.e. proper nouns) have been linked with damage to the most anterior portion of the temporal lobe, the temporal pole (TP). These deficits suggest the TP may mediate storage and retrieval of semantic knowledge specifically for proper nouns. However, neuropsychological evidence from degenerative diseases (e.g. semantic

dementia) suggests that the TP may instead function as a generalized hub for all conceptual knowledge (i.e. common and proper nouns), with response properties graded in relation to semantic demand (response to proper > common nouns). The TP's proximity to air-filled sinuses and superficial musculature has made noninvasive study of this region difficult, precluding consensus regarding even basic distinctions of TP function. We leveraged millisecond-resolution human, intracranial EEG (icEEG) data to critically evaluate these unique-entity (UEM) and general-hub (GHM) models of TP function. If the UEM is accurate, we hypothesize that the TP would respond preferentially to proper nouns. In contrast, the GHM predicts that the TP would respond to all salient stimuli, irrespective of noun class. Data were collected in a large cohort (21 subjects; 12 LH; 9RH; 15 female) performing a visual confrontation-naming task of common objects (common nouns), famous faces (proper nouns), and scrambled control images of the same stimuli (scramble). We observed a transient, early (~200 ms after stimulus onset) increase, bilaterally, in high-frequency broadband gamma activity (BGA; 60-120 Hz; percent change from pre-stimulus baseline of -700 to -200ms) for all three stimuli. However, in the left TP only, peak percent change in BGA was strongest for proper, followed by common, and then scrambled stimuli. In contrast, no significant conditional differences were observed in the right TP. Finally, in the left TP, a subsequent increase in BGA was observed for correctly named common and proper nouns, but not for incorrectly named nouns or scrambled stimuli. Together, these results provide empirical evidence in support of the GHM, with novel insights into the temporal profile of TP activity during visual naming. In sum, our findings reveal an early (~200ms), obligate, and bilateral response to all visual stimuli in the TP, and a continued role for the left TP during both common and proper name retrieval.

Disclosures: C.M. Kadipasaoglu: None. **N. Tandon:** None.

Poster

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Title: Regional difference in characteristics for top-down modulation in the ventral visual stream

Authors: Y.-W. SUNG[1], H. YOON[2], U.-S. CHOI[3], *S. OGAWA[1];
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Abstract: Top-down modulation to low level areas from high cognitive areas has been reported in number of electrophysiology studies. In particular, ventral visual stream has shown area-specific characteristics such as center-peripheral specialization and categorical specialization. In terms of center-peripheral specialization, lateral areas supposed to be more sensitive to center vision and facial like stimuli, whereas medial areas to peripheral vision than building stimulation. There is a possibility that ventral visual stream has similar regional differences in characteristics for top-down modulation. In this study we examined by fMRI a possible difference in top-down modulation depending on areas in the ventral visual region. Top-down modulation is generally known to be dependent on stimuli per se. Here, we intend to examine whether such modulation mechanism seems to exist after the stimuli response, namely the feedback. Participants performed a well-characterized visual and auditory categorization paradigm, in which they had to decide, in combination with line drawings of faces, whether the pitch of frequency-modulated (FM) tones was rising or falling. After the decision the feedback follows either with no interval or 1 second delay. Line drawings of faces with positive and negative emotional cues were used for the feedback provider. We found activations at some areas in early visual and in occipitotemporal regions. The fMRI response signals were different across areas and between non-delay and delay. Notably, the fMRI responses for the delayed feedback showed the shifted time course than for the non-delay at the medial areas of the occipitotemporal region as well as in the fovea and peripheral areas at V1 but not at the lateral areas of occipitotemporal region. This difference in occipitotemporal region might reflect the different feedback characters in the lateral and medial areas of early visual cortices, which seem to be influenced by top-down modulation. This result indicates the area-specific differences to the feedback in the ventral region.

Disclosures: Y. Sung: None. **H. Yoon:** None. **U. Choi:** None. **S. Ogawa:** None.

Poster

792. Visual Processing: Learning, Memory, and Categorization

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Support: NSF Grant 1157121

Title: Activity change in the left fusiform cortex suggests learning in face detection

Authors: *J. E. GOOLD, M. MENG;
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Abstract: The ability to detect a face is the gateway to individual identification and social interaction. Previous research has suggested two possible mechanisms for how the human brain detects a face: 1) the right fusiform gyrus responds categorically to face/non-face images. It will selectively respond in an "all-or-nothing" burst as to whether an image is a face. 2) The left fusiform gyrus responds in a graded manner to how "face-like" an image is. It will estimate how much an image looks like a face, with genuine faces getting the highest response (Meng et al., 2012). To evaluate these possibilities, the present study examines whether training in face/non-face categorization vs. training in face-likeness analysis may improve face detection and change how the brain detects a face. Two types of stimuli were used for training and testing the effect of training respectively. The first set of stimuli consisted of gray-scale (easy to detect) images ranging from no resemblance to faces to genuine faces. The second set of stimuli consisted of two-toned, black and white (hard to detect) Mooney images generated from the gray-scale images (Mooney, 1957). The study contained three parts: First, brain activity was measured by using fMRI for all participants (N=24) when they were shown a randomly chosen half of the set of two-toned (hard) images and instructed to respond 'face' or 'not-face' to each image. Next, participants were randomly split into two groups for training. Both groups viewed the gray-scale (easy) stimuli three times a day for five days. However, the categorical group was instructed to make 'face' or 'not-face' judgments about whether the images were faces, while the graded group was instructed to rate the images on a Likert scale of 1-5 for how "face-like" they were. For the third part of the study, all participants repeated the fMRI scan with the other half of the two-toned (hard) stimuli. Our findings show that when participants were trained categorically, the response in the left fusiform gyrus to the two-toned (hard) images changed from graded to categorical. By contrast, we found no significant change in brain response in the graded group. These results suggest that learning of the face/non-face categorical boundary instead of evaluating face-likeness is critical for improving face detection. Moreover, whereas activity in the right fusiform cortex correlated with face/non-face categorization but remained unchanged, the activity change in the left fusiform cortex underlies the effect of learning in face detection. This suggests complementary functional roles of the two hemispheres in face perception and learning.

Disclosures: J.E. Goold: None. **M. Meng:** None.

Poster

792. Visual Processing: Learning, Memory, and Categorization

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ANR-10-IDEX-0001-02 PSL*

ANR-11-EMCO-00902

Title: Expectation about face identity biases emotion categorization: evidence from behavioral modeling and pupillometry

Authors: *M. EL ZEIN, V. WYART, J. GREZES;
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Abstract: Expectation in perceptual decision making influences neural and behavioral responses by facilitating the processing of expected stimuli (*Summerfield & DeLange, 2014*). During our social interactions, most of our interpretations and decisions are based on past experience and priors about people and events. Particularly, expectations about people's characters and moods build upon previous encounters with these people. Here we aim to identify the mechanisms of identity expectation influence on the categorization of facial expressions during an eye tracking behavioral study including 31 healthy human participants. We manipulated expectations about emotional expressions (Fear and Anger) of identities by presenting subjects with short periods at the beginning of each block where identities (32 in total) expressed either only anger (Anger group) or only fear (Fear group). During the rest of the block, all identities expressed anger and fear equally, while their emotional intensity varied parametrically. Importantly, during both periods, subjects performed an emotion categorization task (Fear or Anger?) and had no explicit warning of any change occurring between the periods. Finally, they reported during a post test whether the 32 encountered identities expressed more anger or fear during the experiment. Increased accuracy for expected stimuli (angry expressions of Anger group and fearful expressions of Fear group) during the unbiased blocks showed that participants integrated the information about stimulus identity although it was manipulated implicitly. Model comparisons characterized the effect by showing that subjects' decision bias rather than their choice sensitivity was influenced by identity expectation: response bias pulled toward anger for the Anger group and toward fear for the Fear group. Subjects were at chance level during the posttest, suggesting that the bias was implicitly induced. Interestingly, the identities they explicitly and incidentally assigned to Fear and Anger in the posttest also strongly biased their decisions throughout task. Pupil dilation tracked both the perceptual evidence to response by decreasing with stimulus intensity and response bias by increasing when subjects responded against their bias (*de Gee et al. 2014*). To conclude, these results imply that both experience (implicit learning of identity/

emotion associations) and incidental associations (spontaneous associations explicitly reported) shape expectations about people's mood (*Todorov et al. 2015*). Further, these expectations shift the decision bias about facial expressions in response-selective, not stimulus-selective structures.

Disclosures: **M. El Zein:** None. **V. Wyart:** None. **J. Grezes:** None.

Poster

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Title: Inter-area signal targeting translaminar processing during successful memory retrieval in macaque temporal cortex

Authors: *M. TAKEDA[1,2], K. W. KOYANO[1], T. HIRABAYASHI[1], Y. ADACHI[1], T. ISHII[1], Y. MIYASHITA[1,2,3];
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Abstract: Memory retrieval in primates is orchestrated by a brain-wide neuronal circuit. To elucidate the operation of this circuit, it is imperative to comprehend neuronal mechanisms of coordination between area-to-area interaction and information processing within individual areas. Converging evidence from neuropsychological, anatomical and lesion studies has suggested that memory processes including consolidation and retrieval are implemented by the interaction between the medial temporal lobe and the domain-specific association cortices. Area

TE, which is part of the temporal association cortex, is adjacent to and interconnected with area 36 (A36) of the perirhinal cortex which is part of the medial temporal lobe. These brain areas are known to engage in the associative representations of long-term memory of visual objects and to play distinct roles in memory retrieval. While the perceptual activity of visual objects emerges earlier in TE than A36, memory retrieval activity for the sought target emerges earlier in A36 than TE, suggesting that a backward signal flows from A36 to TE during memory retrieval. The inter-area signal, if present, would modify local signal processing implemented by laminar neuronal circuits in the target area. To test this hypothesis, we simultaneously recorded from A36 and TE while monkeys performed a pair-association memory task (Takeda et al., 2015). We found two distinct inter-area signal flows during memory retrieval: A36 spiking activity exhibited coherence with low-frequency field activity in either the supragranular or infragranular layer of TE. Of these two flows, only signal flow targeting the infragranular layer of TE was further translaminarly coupled with gamma activity in the supragranular layer of TE. Moreover, this coupling was observed when monkeys succeeded in the retrieval of the sought object but not when they failed. The results suggest that local translaminar processing can be recruited via a layer-specific inter-area network for memory retrieval. Reference Takeda M, Koyano KW, Hirabayashi T, Adachi Y, Miyashita Y. Top-Down Regulation of Laminar Circuit via Inter-Area Signal for Successful Object Memory Recall in Monkey Temporal Cortex. Neuron, 2015, 86 (3), 840-852.

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Poster

792. Visual Processing: Learning, Memory, and Categorization

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Title: Neural correlates of statistical learning in the inferior-temporal cortex of rhesus monkeys

Authors: *S. KUMAR, P. KAPOSVARI, R. VOGELS;
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Abstract: We learn to implicitly extract the statistical regularities in the environment around us, e.g. sequences of stimuli that follow each other (e.g. letters in specific words). In the visual domain, human observers can extract regular sequences of visual stimuli from a continuous stream of visual shapes. The neural correlates of such visual sequence learning are still unclear. Previous electrophysiological studies on visual sequence learning in the macaque inferior temporal (IT) cortex, using pairs (Meyer and Olson, 2011, PNAS) and triplets (Meyer et al, 2014, J. Neurosci) of images, showed stronger neural responses to a stimulus that deviated from the one expected in the learned pair or triplet. In these studies the learned stimulus pairs or triplets were clearly temporally delineated by an inter-sequence interval unlike in behavioral statistical learning studies in which a continuous, uninterrupted stream of stimuli are presented. Furthermore, the separated stimulus sequences were each followed by a reward, which may have aided learning. Here we mimicked behavioral and imaging studies of statistical learning by exposing monkeys to a continuous stream of images. The stimulus stream consisted of 3 fixed sequences of 5 grayscale images each and these 3 short sequences were presented in a random order. We randomly rewarded the monkeys with a fluid reward for fixation and the reward timing was unrelated to the stimulus presentation or identity. After a passive exposure to the sequences for two months, we assessed whether the responses of IT neurons showed a correlate of the sequence learning by introducing deviant stimuli in the fixed standard sets. The deviant stimuli were either stimuli from one of the other 2 short sequences or a stimulus from the same sequence but at a wrong position within that sequence. We compared the multiunit neuronal responses for the deviant stimuli with identical stimuli when presented in the standard, learned sequence. We observed a significant enhancement of the responses to the deviant stimulus and the trailing standard stimuli, when the deviant was either from the same sequence ($p < 0.05$) or from the other two sequences ($p < 0.0005$). The neuronal responses to a second deviant stimulus (which followed the first deviant in the standard set) did not differ significantly from the standard. These results demonstrate that monkey IT cortex, under learning conditions that mimic those of statistical learning in human behavioral and imaging studies, encodes at least part of a learned temporal sequence in which a stimulus is presented.

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Poster

792. Visual Processing: Learning, Memory, and Categorization

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Title: Electrophysiological predictors of an anticipated stimulus during visual sequence learning

Authors: M. SENOUSSI[1,2], *R. VANRULLEN[2,1], L. REDDY[1,2];
[1]Univ. de Toulouse; UPS; Ctr. de Recherche Cerveau et Cognition, Toulouse, France; [2]CNRS, Toulouse, France

Abstract: Learning sequences of events is a fundamental ability, allowing us to remember landmarks on the way to a new job, or to play a song without the sheet music. Anticipation of upcoming stimuli in a known sequence can improve their detection, but the way our brain builds up this directional association between stimuli is poorly understood. Here we investigated whether learning a visual sequence would elicit neural activity patterns selective for the next-to-come stimulus. Sixteen human subjects performed a visual sequence learning task while their neural activity was recorded using Electroencephalography (EEG). Six images from distinct categories (car, pinecone, face, camel, house and phone) were presented in a predictable sequence, as if rotating on a virtual "wheel" composed of 6 black square canvases. In each trial the wheel rotated to the next position for 0.5s, stopped and the central black canvas revealed either the corresponding image (stim trials, 45% of all trials) or a neutral gray square (catch trials, 45% of all trials) for 1s. Then the image turned black again, and the wheel started rotating for the next trial. In randomly interleaved test trials (10% of all trials) the sequence was stopped and subjects reported via button press which of two simultaneously displayed images was to appear next. All images were equalized in 2D Fourier power spectrum. We hypothesized that as a result of learning, brain activity in catch trials (with no image on the screen) should reflect the identity of the image that should have been presented at that point in the sequence; alternately, if no learning occurred all catch trials should be treated similarly by the brain. To uncover selective brain activity we used a Support Vector Machine classifier based on spatial patterns of spectral information (for each time point and oscillatory frequency, the amplitudes across 64 electrodes). To limit the influence of residual activity from preceding stim trials on the classifier performance, we only considered trials preceded by a catch trial. As a first validation of our analysis, we computed classification accuracy during stim trials (image on-screen). On average across subjects, the classifier reached 62% accuracy, with chance level at 16.6% (permutation

test, 10,000 surrogates, p < 10-4). Critically, on catch trials we could also decode above chance the category of the image that should have appeared (19.3 %, p < 10-4), even though only a neutral gray square was on the screen. This ability was mainly driven by high-alpha or low-beta frequencies (11-16Hz). These results show that learning a visual sequence induces selective oscillatory activity in the absence of an anticipated stimulus.

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Poster

792. Visual Processing: Learning, Memory, and Categorization

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Title: Enhanced readout of early visual cortex after perceptual learning measured with fMRI

Authors: *B. JANS[1], V. VAN DE VEN[2], L. WALDORP[3], M. M. BEEN[2], I. BLOEM[4], K. ULUDAğ[2,5], R. GOEBEL[2,5], P. DE WEERD[2,6];
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Abstract: As an explanation of visual skill learning, one class of models emphasizes enhanced readout from low-level areas by high-level areas [1, 2]. To test this idea, 7 human participants performed an easy orientation discrimination task at a fixed orientation difference with gratings at a 1-32% contrast range in a ‘training’ quadrant. Simultaneously, ignored stimuli were shown in an ‘exposure’ quadrant. A third quadrant served as ‘unstimulated’ control. We performed 4-6 3T fMRI scans of V1, V2, and V3 in each participant while they performed the task in the

training quadrant and ignored gratings in the exposure quadrant, or performed an attention demanding task at fixation while ignoring the gratings in both quadrants. During training, the % correct performance increased strongly for lower but not higher contrasts. Before learning, a baseline scan during the fixation task in the training and exposure quadrants confirmed a parametric effect of contrast with the lowest contrast eliciting the lowest fMRI response, whereas in the unstimulated quadrant no fMRI response was observed for any contrast. Interestingly, during the first task performance, there was a parametric effect of contrast not only in the training quadrant, but also in the unstimulated quadrant. Furthermore, fMRI responses to lower contrasts in the training quadrant showed a gradual increase over the course of learning. Once participants reached asymptotic performance, fMRI response amplitudes to lower contrasts equaled those evoked by the highest contrasts. The same trend over sessions was also present in the simultaneously measured fMRI responses in the unstimulated quadrant, although in that quadrant, when attention was at fixation, there was never any response associated with the co-occurring stimuli in the trained quadrant. V1, V2 and V3 showed similar results; trends in exposed quadrant were not significant. Based on findings in training and unstimulated quadrants, our results show that bottom-up responses to ignored stimuli are limited to the site of stimulation. Moreover, we suggest that fMRI responses during task performance reveal a correlate of read-out, which appears to be spatially aspecific, and which show increased amplitude to low contrasts in a manner correlating with behavioral performance increments during training. The readout component revealed here may contribute to spatial generalization of early perceptual learning [3]. [1] Law & Gold, Nat. Neurosci., 2008; [2] Ahissar & Hochstein, Nature, 1997; [3] Xiao et al., Current Biology, 2008.

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Poster

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Support: IRSC Grant MOP111003

Title: Donepezil improves perceptual-cognitive performance of healthy young adults

Authors: ***M. CHAMOUN**[1], F. HUPPÉ-GOURGUES[1], I. LEGAULT[1], P. ROSA-NETO[2], J. FAUBERT[1], E. VAUCHER[1];

[1]Optometrie, Univ. De Montreal, Montreal, QC, Canada; [2]Douglas Res. Ctr., McGill Univ., Montreal, QC, Canada

Abstract: Donepezil, a cholinesterase inhibitor that acts by blocking the breakdown of acetylcholine (ACh) in the synapse, is used in the treatment of Alzheimer's disease. Donepezil has been demonstrated to increase perceptual learning by improving the performance in a specific repetitive training task. As ACh is involved in cortical plasticity and experience-dependent increase in cortical activity, this suggests that a cholinergic enhancement through donepezil could be used to improve visual performance in healthy and visually impaired persons. Our study examines whether repetitive acute administration of donepezil improves perceptual-cognitive performance in a highly demanding attentional task defined by visual tracking of moving spheres in a 3D space over five consecutive weeks. A double-blind, placebo controlled design was used to evaluate the effect of cholinergic enhancement - donepezil administration (5 mg, given per os) - on visual attention or visual detection. 10 young healthy adults were enrolled in each group. The task was performed 3 hours after the donepezil (or placebo) intake to synchronize with the peak plasma concentration of the drug. The multifocal attention of the participant was tested by the multiple object tracking task 3D-MOT (Legault and Faubert, 2012). During this perceptual-cognitive task, the observer is required to simultaneously track multiple moving items among distracters in a dynamic virtual reality environment. The task is repeated once a week during 5 weeks to test the effect of learning. It has been proven that performing 3D-MOT speed task over consecutive weeks results in an increase in performance of healthy young adults. For our experimental design this significant increase in performance from the first week baseline was revealed starting the 4th session for donepezil group, in comparison with control group who only showed significant improvement in the last session (5th). Motion and direction identification thresholds for the first order and second order visual detection before and after donepezil intake were however not altered. Our results show that an acute 5mg dose of donepezil improves perceptual-learning performance for healthy young participants in a highly demanding perceptual-cognitive task. Additional studies are needed to better define the involvement of acetylcholine enhancement on perceptual learning/attentional tasks. The long-term goal is to improve, for rehabilitation purposes, the visual performance of people having a visual or attention deficit.

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Poster

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NEI

Title: Learning for perception and action: motion prediction in humans and non-human primate pursuit

Authors: T. MUKHERJEE[1], G. ZAKHARY[1], W. BIALEK[2], *L. C. OSBORNE[1];
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Abstract: Prediction is one of the fundamental problems in neural computation. Much of what we admire in expert human performance is predictive in character: the point guard who passes the basketball to a place where his teammate will arrive in a split second, the chess master who knows how moves made now will influence the end game two hours hence, the investor who buys a stock in anticipation that it will grow in the year to come. More generally, we gather sensory information not for its own sake but in the hope that this information will guide our actions. But acting takes time, and sense data can guide us only to the extent that those data inform us about the state of the world at the time of our actions. In short we learn the likelihood of future events and use those predictions to guide behavior. There are limits on the accuracy of prediction, and here we ask how close organisms come to optimal performance. We use pursuit eye movements, along with perceptual reports, as a model system in which to explore the learning of probabilities from examples. We have created a simple task where we control the elements of randomness in prior experiences and observe its effect on learning rates for pursuit and perception. We find that subjects make anticipatory eye movements in proportion to confidence in future target movements. We use the anticipatory movements as a metric to quantify motor learning, and, in human subjects, compare to perceptual predictions. Generating target motion sequences from different probability "landscapes", we ask how much information about the underlying distribution is incorporated into predictive behavior compared to an ideal observer. We find that probability learning is adaptive, changing how past experiences are weighted to guide future action based on the correlations in motion probabilities over time.

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Poster

793. Spatial and Feature-Based Attention

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Topic: D.04. Vision

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Bert and Ethel Aginsky Research Scholar Award (Salk Institute)

Gatsby Charitable Foundation

Title: A mouse model for selective spatial attention

Authors: *E. MCBRIDE, E. CALLAWAY;
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Abstract: Attention focuses our limited perceptual resources toward the most relevant stimuli in a distracter-filled environment. Work in primate visual cortex has shown that attending to a location in the visual field enhances neural responses and perceptual sensitivity to stimuli presented there and suppresses responses and sensitivity to stimuli elsewhere. However, neural recording methods available for use in primates are limited in their ability to probe neural circuitry, thus the specific mechanisms and circuits that influence attention and behavior remain mostly unknown. A more detailed description of these circuits requires simultaneous recordings from large populations of neurons in different brain regions, direct manipulation of the activity of specific neuron types, and observation of associated behavioral changes. Genetic tools for selective targeting and manipulation of identified circuit components in the mouse make these experiments possible. When a mouse runs, neural responses are enhanced in response to a visual stimulus, similar to the effect of attention. The circuit mediating this effect has been shown to involve cholinergic projections from the basal forebrain. However, this is likely a global alertness state primarily due to locomotion-induced bottom-up processes. No study yet has examined selective spatial attention in mice, which is likely mediated by top-down projections encoding a decision to selectively attend. To investigate how neural circuitry mediates and is affected by attention, I have successfully trained mice to report the termination of an attended visual stimulus in a specific spatial location, and ignore distracter stimuli. Moving bars display on two screens, one in front of each eye, and the mouse's attention is cued to a particular side. Stimuli are presented simultaneously, but have different durations, and the mouse reports when the target stimulus ends by licking a sensor. In order to perform above chance, the mouse must attend to the target and ignore the distracter. This task will enable us to combine

electrophysiology with optogenetic methods to measure receptive field properties and visual responses under attended and unattended conditions and to probe the role of specific neuronal populations in the control of attention.

Disclosures: E. McBride: None. **E. Callaway:** None.

Poster

793. Spatial and Feature-Based Attention

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Topic: D.04. Vision

Support: NIDCD 1F31DC013708-01A1

Title: The impact of visual salience on noise correlations in the barn owl optic tectum

Authors: *D. TOTTEN, W. M. DEBELLO;
UC Davis, Davis, CA

Abstract: The deep layers of the optic tectum integrate information across modalities to generate a topographic map of space. The spatial and salience tuning of single units in the barn owl optic tectum have been well characterized; however the simultaneous responses in populations of neurons have not been described. We have used multi-electrode recordings in awake barn owls to explore how simultaneously recorded neurons change their firing rates, spatial tuning, response variance and noise correlations in response to changes in stimulus salience. The results demonstrate that there are changes in inter-neuronal noise correlations that can not be accounted for by changes in firing rate or changes in spatial tuning. The impact of these correlations on the ability of theoretical linear decoders to estimate stimulus location given neural responses was investigated. These results suggest that while spike count correlations are prevalent and dynamically regulated in the optic tectum, they do not have a measurable impact on the capacity of the network to localize visual stimuli. Finally, these experiments establish a framework for investigating the potential role of noise correlations in stimulus competition, bimodal processing, plasticity and learning.

Disclosures: D. Totten: None. **W.M. DeBello:** None.

Poster

793. Spatial and Feature-Based Attention

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Topic: D.04. Vision

Support: National Eye Institute Intramural Research Program at the National Institutes of Health

Title: Effects of superior colliculus inactivation on visual attention at the fovea

Authors: *R. J. KRAUZLIS, A. R. BOGADHI, A. BOLLIMUNTA;
Lab. of Sensorimotor Res., Natl. Eye Inst., Bethesda, MD

Abstract: Clinical and experimental studies show that the superior colliculus (SC) plays a crucial role in visual spatial attention. Specifically, we have previously demonstrated that inactivation of the superior colliculus (SC) in monkeys causes large deficits in perceptual decisions based on visual signals located in the affected part of the visual field. Because these previous studies tested attention at peripheral locations, it is not known whether the role of the SC is limited to directing attention away from the fovea, or whether the SC is also important for visual attention at the fovea, where much of primate vision takes place. We have now investigated this issue by measuring performance on a foveal visual task, before and during SC inactivation. Two rhesus macaques were trained to perform a foveal change-detection task, which required them to continuously fixate a central visual stimulus for the duration of each trial. At a randomized time, the luminance of the fixated stimulus decreased, and the animal's task was to release the joystick immediately after this change in order to receive a juice reward. The size of the luminance decrement was adjusted to be at each animal's perceptual threshold. We measured performance before and during injection of muscimol, a GABA agonist, into the intermediate layers of the SC centered at different retinotopic locations. The extent of the inactivation caused by the muscimol injection was estimated from the decreases in the peak velocities of saccades to visual targets across the visual field. Performance on the foveal change-detection task was significantly impaired during SC inactivation, but only during inactivation experiments that substantially affected the foveal part of the SC retinotopic map. In three experiments in the two animals, the percentage of correctly detected luminance changes was ~40% during inactivations that included the central ~3 degrees of the SC map, compared to ~62% before the inactivation. These findings suggest that the role of the SC in the control of attention is not restricted to peripheral parts of the visual field or only to shifting attention to new stimuli, but also includes sustained visual attention at the fovea.

Disclosures: R.J. Krauzlis: None. **A.R. Bogadhi:** None. **A. Bollimunta:** None.

Poster

793. Spatial and Feature-Based Attention

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Topic: D.04. Vision

Support: National Eye Institute Intramural Research Program at the National Institutes of Health

Title: Attention-related BOLD and single-unit modulation with and without superior colliculus inactivation

Authors: *A. BOLLIMUNTA[1], A. R. BOGADHI[1], D. A. LEOPOLD[2], R. J. KRAUZLIS[1]; [1]Lab. of Sensorimotor Res., Natl. Eye Inst., Bethesda, MD; [2]Lab. of Neuropsychology, Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: The superior colliculus (SC) contributes to visual spatial attention through mechanisms that can be dissociated from the classic attention-related modulation in visual cortex (Zenon & Krauzlis, 2012). It is not yet known whether SC influences attention-related activity in the lateral intraparietal area (LIP) or frontal eye fields (FEF). We have now tested this by doing fMRI and single-unit recordings in monkeys during a spatial attention task. We used the same behavioral tasks and inactivation methods for both the fMRI and single-unit experiments. The tasks required the monkey to respond to stimulus changes in one of three different conditions that were interleaved within each run. These conditions included Baseline (B), Foveal Attention (FA) and Peripheral Attention (PA). In B block trials, the monkey released a lever in response to the unpredictable dimming of a central fixation point. FA block trials were similar to B block trials but also included a peripheral motion-change stimulus as an irrelevant distracter. In PA block trials, the fixation point did not dim, and the peripheral motion-change was the relevant stimulus. The task of the monkey was to maintain central fixation and to report the peripheral motion-change by releasing a lever to get a juice reward. To reversibly inactivate the SC inactivation, we injected muscimol in the intermediate and deep layers. In the fMRI experiments, control and inactivation data were collected on interleaved days. Mean % change in BOLD during PA and FA blocks was used to calculate the Attention-related Modulation Index (AMI). In the single-unit experiments, recordings were made with tetrodes in FEF ipsilateral to the inactivated SC. Data were collected from units whose receptive fields overlapped with the inactivated region, before and during inactivation. During inactivation, performance was significantly impaired for stimuli in the contralateral region. Nonetheless, both fMRI and single-unit data revealed a normal attention modulation of cortical areas, consistent with previous results (Zenon and Krauzlis, 2012). The attention-related BOLD modulation was intact not only

in visual cortical areas MT/MST (AMI control: 0.4; inactivation: 0.38), but also in areas LIP and FEF (AMI control: 0.47, 0.57; inactivation: 0.39, 0.58). Consistent with this observation, preliminary single-unit recordings in FEF revealed that attention-related modulation of neural firing rate remained intact during inactivation (AMI control: 0.18, n = 6; inactivation: 0.21, n = 8). These findings suggest that the SC contributes to spatial attention through circuits outside visual cortex and the well-known fronto-parietal network.

Disclosures: **A. Bollimunta:** None. **A.R. Bogadhi:** None. **D.A. Leopold:** None. **R.J. Krauzlis:** None.

Poster

793. Spatial and Feature-Based Attention

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Topic: D.04. Vision

Support: NIH Grant EY018683

Title: Searching for a frequency based signal for attention

Authors: *V. L. MOCK, J. R. HEMBROOK-SHORT, F. BRIGGS;
Physiol. and Neurobio., Geisel Sch. of Med. At Dartmouth, Lebanon, NH

Abstract: Local field potentials (LFPs) provide information about a local population of neurons and can be used to explore how the activity of these neurons encodes specific cognitive functions. We are interested in exploring these signals to determine how information carried in specific frequency bands is linked to visual attention. We examined how attention alters specific frequency modulations in LFPs across the layers of primary visual cortex (V1) and coherence between the visual thalamus (lateral geniculate nucleus or LGN) and V1. We recorded LFPs through electrodes placed within retinotopically-aligned regions of the LGN and V1 in awake-behaving monkeys performing a contrast change detection task that required covert shifts in visual spatial attention. We observed consistent peaks in the power spectra of V1 LFPs at alpha and beta frequencies with a modest peak in gamma. We observed some laminar differences in alpha and beta power between layers 4 and 6 that were most pronounced during visual stimulus presentation periods of the trials. Further, although all layers show an increase in LFP amplitude following stimulus onset, regression fits of LFPs showed a greater amplitude increase in layer 4 compared to layer 6. Modulations in gamma band activity were different from those of alpha and beta bands in a number of ways, suggesting that modulations at gamma frequencies carry more

attentional information compared to modulations in alpha and beta bands. In contrast to alpha and beta band power, which increased during the visual stimulus period, gamma power was higher during the cue period. Additionally, we observed an attentional modulation of the phase of V1 LFPs with the most pronounced phase advance with attention at gamma frequencies. When we examined coherence between V1 contacts and LGN contacts, alpha and beta coherence appeared to be related to the visual stimulus, whereas gamma coherence was strongest during the cue phase. Furthermore, gamma coherence peaked at deep contacts corresponding to layer 6, which contains corticogeniculate neurons. Together, these results support the idea that the gamma frequency band may specifically convey attention signals within V1 and between V1 and LGN.

Disclosures: V.L. Mock: None. **J.R. Hembrook-Short:** None. **F. Briggs:** None.

Poster

793. Spatial and Feature-Based Attention

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Support: NIH Grant F32EY023165

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Title: Attentional modulation of V1 neurons depends on physiological response properties in the primate

Authors: *J. R. HEMBROOK-SHORT, V. L. MOCK, F. BRIGGS;
Physiol. and Neurobio., Geisel Sch. of Med. at Dartmouth, Lebanon, NH

Abstract: Attentional modulation of firing rate varies across visual cortical neurons whereby attention can lead to increases or decreases in neuronal firing rate. However, whether the physiological response properties of individual neurons contribute to this variation is not known. In order to explore potential sources of variation in attentional modulation across neurons, we examined a variety of visual response properties for neurons spanning the cortical layers of primary visual cortex (V1) of awake-behaving monkeys. A 24-contact linear U-probe (Plexon Inc.) was used to record single-unit activity while animals performed a contrast-change discrimination task, which required covert shifts in visual spatial attention. The visual physiology of recorded single-units was determined based on their responses to drifting sinusoidal gratings

varying in contrast, orientation, size and spatial and temporal frequency. Attentional modulation was assessed by comparing neuronal firing rates across trials in which animals attended towards versus away from a visual stimulus that overlapped recorded receptive fields. Over our entire population of well-isolated units in V1, there was a small but significant positive shift in attentional modulation of firing rate and a significant increase in the signal-to-noise ratio of spike waveforms on attention trials compared to tuning trials in which animals were simply required to fixate and ignore grating stimuli. Additionally, we noted wide variation in attentional modulation of firing rates with many V1 neurons demonstrating reduced firing rates with attention. We discovered a number of visual physiological response properties that partially explain this observed variability. The strongest predictor of attentional modulation was the f1-to-f0 ratio with complex cells showing significantly greater attentional modulation of firing rate compared to simple cells, which were suppressed by attention on average. Sharpness of orientation tuning and strength of surround suppression also predicted attentional modulation of individual V1 neurons. Finally, neurons most selective for the stimulus feature modulated in the discrimination task were most strongly enhanced by attention. Thus, match between feature selectivity and task type may also be a predictor of attentional modulation.

Disclosures: **J.R. Hembrook-Short:** None. **V.L. Mock:** None. **F. Briggs:** None.

Poster

793. Spatial and Feature-Based Attention

Location: Hall A

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Topic: D.04. Vision

Title: The effects of attentional field size on neuronal population responses in V1 of behaving monkeys

Authors: ***M. GADOT**, I. SHAMIR, H. SLOVIN;
Gonda Multidisciplinary Brain Res. Ctr., Bar-Ilan Univ., Ramat Gan, Israel

Abstract: Spatial selective attention allocates the brain's resources to process certain location (or locations) in the visual field, where stimuli can appear. Ample evidence demonstrated that visual attention facilitates perception and improves behavioral performance; however the neuronal mechanisms underlying spatial attention are not fully understood. To investigate the neural correlates of spatial attention we used voltage sensitive dye (VSD) imaging and measured neural population responses from the primary visual cortex (V1) of behaving monkeys. We trained two macaque monkeys to perform a covert spatial attention task, where a briefly presented spatial cue

(SC) indicated with high reliability to the location of a variable contrast target (focal attention). In addition, we manipulated the attentional field by presenting multiple SCs simultaneously (distributed attention). Our behavioral results show improved performance under focal attention in respect to catch trials (invalid trials) and in the distributed condition, performance was better than invalid trials, but lower than the focal attention condition. In addition RTs were shorter in focal attention then on invalid cueing. We investigated the effect of spatial attention on the signal to noise ratio (SNR) of the neuronal responses. The VSD signal revealed that attention increased the population activity of V1 neurons. Neuronal responses in the imaged area were enhanced for the attend-in condition, relative to the attend-away condition. This attentional modulation persisted long after the SC was turned off. Furthermore, in the distributed attention condition, the attentional modulation was smaller compared to the attend-in condition. We also found that relative to the distributed condition, the activity in the attend-in condition was enhanced in regions retinotopicaly corresponding to the SC and its surrounding region but this enhancement declined at regions located more remotely from the SC. Finally, we tested the effect of attention on the neuronal variability. We calculated the trial-to-trial variability and noise correlation in the attend-in, attend-away and distributed conditions, but could not find a significant attentional effect. To conclude, spatial attention induces increased responses of V1 neurons and modulates the attentional field size. Our results therefore, support the limited capacity hypothesis.

Disclosures: **M. Gadot:** None. **I. Shamir:** None. **H. Slovin:** None.

Poster

793. Spatial and Feature-Based Attention

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Topic: D.04. Vision

Title: Attentional modulation of V1 population responses to shapes and natural scenes

Authors: *P. JENDRITZA[1,2], A. E. LAZAR[3], L. KLEIN[3,2], W. SINGER[3,4,1];
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Abstract: Most of our understanding about the function of the primary visual cortex (V1) relies on studies of individual neurons stimulated with response-tailored visual input. However, it is not yet clear how populations of cells act together to perform the computations necessary for processing complex visual scenes. Inspired by concepts from machine learning, we used a naive

Bayesian classifier to decode stimulus identity from both multi unit (MUA) population activity and band-limited gamma power in a top-down attention paradigm. Data were obtained through chronic recording techniques from two adult male rhesus macaques (Macaca mulatta) implanted with a microdrive containing 32 independently movable electrodes in V1. Naturalistic scenes, shapes and scrambled control stimuli were used to evoke stimulus-specific population responses. The temporally resolved classification of stimulus identity for each task condition (attention outside the receptive fields vs. attention inside the receptive fields) revealed that both MUA activity and gamma oscillations contained information about the visual stimuli and were modulated by attention. Firing rates were increased (Chalk et al. 2010) while the ramp-up in gamma band power during the task (following a 'hazard rate' function) was decreased with attention. Interestingly, oscillatory responses to the naturalistic scenes and shapes differed markedly from the responses to the control images. Visual stimulation with phase scrambled control images or noise images diminished the observed ramp-up in gamma band power. Moreover, the relationship between MUA response magnitude and decoding performance did not follow simple linear characteristics. The decoding performance reached a maximum at the moment of stimulus change (30° rotation of the image), despite a lower firing rate compared to stimulus onset. This suggests a complex relationship between firing rate and information content.

Disclosures: **P. Jendritza:** None. **A.E. Lazar:** None. **L. Klein:** None. **W. Singer:** None.

Poster

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Topic: D.04. Vision

Support: NIH Grant K99EY025026

Title: Laminar organization of visually evoked gamma power in area V4

Authors: *M. P. JADI, A. S. NANDY, T. J. SEJNOWSKI, J. H. REYNOLDS;
Salk Inst., La Jolla, CA

Abstract: Precision of spike times is crucial for information coding in the cortex. Gamma bursts (30-100 Hz) in cortical activity are thought to co-ordinate spike times, thus regulating information transmission. In the visual cortex, visual stimulation has been shown to elevate gamma power in the local field potentials (LFP) and spatial attention has been shown to further enhance this. In visual area V1, elevated gamma power shows a layer specific signature along

the anatomically identified supra, input and deep layers that terminate and initiate distinct input and output pathways. However, the laminar distribution of enhanced gamma power is not well understood in area V4. Also unknown is the layer specificity of attentional modulation of gamma. Using laminar array electrodes, we recorded electrophysiological activity while a monkey performed an attention-demanding task. We identified the three layers using current source density estimates and characterized visually induced gamma power in each. Understanding the layer specificity of attentional modulation of gamma power will facilitate a more complete understanding of their role in cortical processing.

Disclosures: **M.P. Jadi:** None. **A.S. Nandy:** None. **T.J. Sejnowski:** None. **J.H. Reynolds:** None.

Poster

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Title: Laminar organization of attentional modulation in area V4

Authors: A. S. NANDY, J. J. NASSI, *J. H. REYNOLDS;
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Abstract: In order to flexibly adapt to behavioral demands, the brain needs to rapidly modulate the operating mode of the underlying cortical circuits and thereby control the way information is routed. For example, when an observer directs visual attention to a behaviorally relevant stimulus, this reconfigures cortical circuits to selectively process information about the attended stimulus. Tasks that control attention thus provide a powerful way to manipulate cortical information processing. Traditional single unit electrophysiology has provided key insights into the probable neural mechanisms underlying attention in macaque visual area V4, including modulation of mean firing rate and reduction in correlated variability among pairs of simultaneously recorded units. These changes in neuronal response are thought to result from feedback signals generated in attentional control centers, which impinge on the laminar circuits of the visual cortices. To gain insight into the role of laminar circuits in this transformation one must measure the laminar profile of attentional modulation. To do so, the laminar electrode must run down the cortical column and it must therefore be positioned perpendicular to the cortical

surface. In V4 this is a challenge because V4 straddles a narrow gyrus, with only a narrow strip of cortex that lays flat beneath the calvarium. Here, we replaced the native dura with a silicone based optically clear artificial dura. This allowed us to very precisely target laminar array electrodes to pass down the cortical column, normal to the cortical surface. We recorded activity while a monkey performed an attention-demanding task. We obtained receptive field maps down the laminar contacts that were well aligned, and clear current-source-density (CSD) maps, both indicating that the electrode was well aligned with the cortical column. We used CSD maps to distinguish the laminar position (granular, infra-granular, supra-granular) of each channel, and found differential modulation of sensory gain and correlated variability across layers, which will be useful in constraining laminar circuit models of selective attention.

Disclosures: **A.S. Nandy:** None. **J.J. Nassi:** None. **J.H. Reynolds:** None.

Poster

793. Spatial and Feature-Based Attention

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Support: EY022529

EY005911

Title: Graded population activity in area V4 during cued and uncued spatial attention

Authors: ***J. P. MAYO**[1], J. H. R. MAUNSELL[2];
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Abstract: Studies of the neuronal mechanisms of visual spatial attention have relied on the cueing paradigm for decades. Validly cued responses occur during trials where the event occurs at the cued location and invalidly cued responses occur when the event occurs at the unexpected location. Validly and invalidly cued trials are used to measure the effects of attending and not attending to a stimulus location. But human psychophysicists also frequently include an uncued, or neutral, condition where the task event is equally likely to occur at either stimulus location. The uncued condition may better capture the uncertainty inherent in our natural environment and therefore could be a useful tool for studying attention-related changes in neuronal activity. Human performance in the uncued condition is usually better than in the invalidly cued condition

and worse than in the validly cued condition. From this evidence, it is reasonable to expect that neuronal activity in the uncued condition to be similarly intermediate. However, prominent theories of visual attention propose a singular focus of attention such that neuronal responses in the uncued condition would function in a binary manner, exhibiting valid-like or invalid-like patterns of activity at any moment. To study uncued spatial attention, we recorded from populations of neurons in visual area V4 in ~30 recording sessions in two monkeys trained to detect a change in orientation at one of two possible stimulus locations. We interleaved blocks of validly cued, invalidly cued, and uncued trials in each recording session and measured changes in average firing rate and neuronal correlations. We found that firing rates in the uncued condition were lower than those of the validly cued condition but higher than the invalidly cued condition, consistent with the intermediate effects of uncued attention on the animal's behavior. Likewise, neuronal correlations were strongest when the stimulus was unattended, intermediate when uncued, and weakest when attended. Our work supports the hypothesis that neuronal populations in area V4 function in a graded, continuous manner to represent the validity of cued and uncued spatial attention.

Disclosures: **J.P. Mayo:** None. **J.H.R. Maunsell:** None.

Poster

793. Spatial and Feature-Based Attention

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Topic: D.04. Vision

Title: Implicit associations between achromatic cues and spatial attention

Authors: *A. T. MARIN[1], S. A. DREW[2];
[2]Psychology, [1]California State University, Northridge, Northridge, CA

Abstract: Random events seen within our external environment, when repeated, tend to exhibit statistical regularity. Past research has suggested both bottom-up and top-down mechanisms are involved in the documented relation between spatial attention and emotion. Research also suggests the same for achromatic perception and emotion. In this study, we investigated potential low-level behavioral mechanisms underling the relation between achromatic perception (e.g. black and white) and vertical spatial attention (e.g. bottom and top). Thirty participants were tested in a spatial configuration search task that was programmed using the computer software program MATLAB. The task was to locate a single target “T” amongst twelve distracter “Ls”. The background (e.g. black and white) and location of the target (e.g. top and bottom of the

display) varied trial to trial. Results show a significant interaction between the background color and target location in terms of reaction time, $F(1, 29) = 15.57$, $p = .001$, partial $^2 = .35$. Participants were significantly faster in identifying a bottom target when cued with a black screen compared to a white screen. Participants were also faster in identifying a top target when cued with a white screen compared to a black screen. There were also significant main effects of location, $F(1, 29) = 5.59$, $p = .025$, partial $^2 = .16$, but not of background, $F(1, 29) = 2.44$, $p = .129$, partial $^2 = .08$. In order to follow up on these significant findings, a second experiment was conducted in order to separate the co-occurrence of the black and white backgrounds from the visual search task, which returned no significant findings. Theoretical implications are discussed as well as future directions that are in line for the next phase of data collection. Taken together, these results suggest an implicit relationship between achromatic perception and vertical spatial attention. *Keywords:* Visual & Spatial Attention, Statistical Regularities, Achromatic Perception, Natural Scene Statistics

Disclosures: A.T. Marin: None. **S.A. Drew:** None.

Poster

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ONR N00014-14-0670

Title: Feature-based attention regulates long-range neural interactions in monkey area V4

Authors: *R. XIA, S. GUAN, D. SHEINBERG;
Dept. of Neurosci., Brown Univ., Providence, RI

Abstract: Feature-based attention facilitates the representation of visual objects that share attended features regardless of their spatial location. While most studies have focused on the attentional effects at the single neuron level, the underlying network mechanisms remain poorly understood. Inter-neuronal synchrony, as a hypothetical indicator of neural interactions, provides a novel perspective for investigating the network dynamics of attention regulation. Recent studies have shown that attention not only regulates the firing of individual neurons, but also dynamically modulates the temporal coherence between neurons. For instance, in visual area V4,

selective attention enhances the pairwise synchrony when both neurons' receptive fields (RF) overlap with the attended location (Fries et al. 2001). However, these neurons can be physically close to each other due to the retinotopic structure of V4. It remains unclear whether and how feature-based attention regulates the long-range horizontal interactions between neurons with distinct RFs across visual field. To study the network dynamics of feature-based attention in a larger scale, we recorded the neural activity simultaneously from multiple sites in monkey area V4 using a 32-channel Gray Matter drive while the monkey performed a cued visual search task. In the task, a color cue (colored spot) or an orientation cue (black-white Gabor patch) was initially shown at the fixation location to indicate the feature of the target. Following cue offset, two Gabor stimuli with different orientations and colors appeared at opposite directions. A saccade to the target location after the stimulus disappearance was rewarded with juice. Our preliminary results showed that the cue-induced attention regulated both the firing rate and local field potential (LFP) of the recorded population. Neurons/channels selective to cued features were more likely to have higher firing rate and gamma-band LFP power in response to the onset of visual stimuli. More strikingly, some recorded channels showed enhanced LFP-LFP coherence during and after the cueing period, even between those preferring foveal and peripheral locations. Furthermore, using a classifier to decode the feature information from different types of neural signals, it appears that pairwise synchrony plays a role in coding the attended feature, but does not contribute to representing target location. Our ongoing project aims to explore how feature-based attention regulates the horizontal interaction pattern based on the feature tuning of neurons, and our network-level analysis will provide insights to understanding the general mechanism of top-down regulation.

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Poster

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Title: Maintenance of spatial information modulates the correlated variability of MT neurons based on their spatial selectivity

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Abstract: Previous studies have shown that maintaining spatial information improves the discrimination of visual targets at the remembered location.Changes in the correlations in trial-to-trial variability of pairs of extrastriate neurons (noise correlations) have been proposed as a means for improving visual discrimination. We studied how memory-related spatial signals modulate the correlated activity of pairs of neurons within extrastriate areas, and the degree to which these modulations depend on the similarity between the spatial and feature selectivity of the two neurons. In two macaque monkeys, multiple neurons in the middle temporal area (MT) were simultaneously recorded using 16-channel linear array electrodes. The spatial selectivity of the neurons was quantified by measuring their response to probes presented in a 7x7grid centered around their estimated receptive field (RF). Feature selectivity was measured in a separate task in which moving gratings with 8 different directions of motion were presented within the neuron's RF. To test whether the maintenance of spatial information alters the correlated variability of these neurons, we then recorded their activity during the memory guided saccade task. The animal had to remember the location of a target and maintain fixation throughout a 1s delay period, then saccade to that location at the end of the trial. The noise correlations between pairs of MT neurons were measured both prior to target presentation and during the memory period of the task. Pairs of neurons were categorized based on whether the remembered location fell within one, both, or neither of the neurons' RFs. Our results indicate that maintenance of spatial memory changes the correlations in activity between pairs of neurons, and that this change depends on the arrangement of the neurons' RFs relative to the remembered location. In contrast, the degree of feature similarity within a pair had negligible effect on the changes in their noise correlation during memory maintenance. These findings demonstrate how the top-down spatial signal interacts with the spatial and feature preferences of neurons within extrastriate areas, providing a more complete picture of how these changes in correlated activity can contribute to enhancing visual representations.

Disclosures: Y. Merrikhi: None. **M. Parsa:** None. **B. Noudoost:** None.

Poster

793. Spatial and Feature-Based Attention

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 793.15/N30

Topic: D.04. Vision

Support: Deutsche Forschungsgemeinschaft, Collaborative Research Center 889, Project C04

Title: Response modulations by spatial but not by feature-based attention are correlated with reduction in bursty firing in area MST

Authors: *C. XUE[1], B. S. KRISHNA[1], S. BALONI[1], D. KAPING[1,2], S. TREUE[1];
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Abstract: Visual attention is known to modulate the firing rate of neurons in many areas of the primate visual cortex. In addition the temporal pattern of neuronal activity can also vary according to behavioral context. In particular, the burstiness of firing patterns of V4 neurons has been shown to decrease when spatial attention is directed into their receptive fields (Anderson, Mitchell and Reynolds, Nat. Neurosci., 2013). However, it remains unclear if this result extends to other brain regions and types of attention, and how the variation in burstiness relates to the well-known modulation of firing rate by attention. Here, we analyzed extracellular neuronal data recorded from area MST of two rhesus monkeys (Macaca mulatta) while they performed a task in which they had to respond to a brief motion direction change in one (the 'target') of two moving random dot patterns (RDPs), while ignoring similar changes in the other RDP (the 'distractor'). When the RDPs moved in the preferred direction of the recorded neuron, comparing the responses when the RDP in the receptive field (RF) was the target or the distractor enabled us to examine the effects of spatial attention. Similarly, when the distractor was in the RF and moved in the preferred direction, comparing the responses when the distractor RDP outside the RF moved either in the preferred or anti-preferred direction enabled us to examine the effects of feature-based attention. Both spatial attention into the RF (relative to spatial attention directed outside the RF) and feature-based attention to the preferred direction (relative to the non-preferred direction) enhanced the firing-rate of MST neurons, as expected. However, while spatial attention also led to a concurrent net reduction in burstiness (as reported earlier from V4), feature-based attention was not associated with a clear effect on burstiness. This lack of a net effect on burstiness could not be explained by the fact that feature-based attention's effect on firing-rate was smaller than that of spatial attention. Our results confirm the effects of spatial attention on burstiness in MST, and indicate that spatial and feature-based attention have different effects in MST neurons.

Disclosures: C. Xue: None. **B.S. Krishna:** None. **S. Baloni:** None. **D. Kaping:** None. **S. Treue:** None.

Poster

793. Spatial and Feature-Based Attention

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Title: "Everything you always wanted to know about fitting tuning curves* (*But were afraid to ask)": model-free characterization of tuned responses and of their attentional modulation

Authors: *M. HELMER[1,2], V. KOZYREV[3,4], V. STEPHAN[4,2], S. TREUE[4,2], T. GEISEL[5,2], D. BATTAGLIA[6,2];
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Abstract: Tuning curves are the functions that relate the responses of sensory neurons to various values within one continuous stimulus dimension (such as the orientation of a bar in the visual domain or the frequency of a tone in the auditory domain). They are commonly determined by fitting a model e.g. a Gaussian or other bell-shaped curves to the measured responses to a small subset of discrete stimuli in the relevant dimension. However, as neuronal responses are irregular and experimental measurements noisy, it is often difficult to determine reliably the appropriate model from the data. We illustrate this general problem by fitting diverse models to representative recordings from area MT in rhesus monkey visual cortex during multiple attentional tasks involving complex composite stimuli. We find that all models can be well-fitted, that the best model generally varies between neurons and that statistical comparisons between neuronal responses across different experimental conditions are affected quantitatively and qualitatively by specific model choices. As a robust alternative to an often arbitrary model selection, we introduce a model-free approach, in which features of interest are extracted directly from the measured response data without the need of fitting any model. In our attentional datasets, we demonstrate that data-driven methods provide descriptions of tuning curve features such as preferred stimulus direction or attentional gain modulations which are in agreement with

fit-based approaches when a good fit exists. Furthermore, these methods naturally extend to the frequent cases of uncertain model selection. We show that model-free approaches can identify attentional modulation patterns, such as general alterations of the irregular shape of tuning curves, which cannot be captured by fitting stereotyped conventional models. Finally, by comparing datasets across different conditions, we demonstrate effects of attention that are cell- and even stimulus-specific. Based on these proofs-of-concept, we conclude that our data-driven methods can reliably extract relevant tuning information from neuronal recordings, including cells whose seemingly haphazard response curves defy conventional fitting approaches.

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Poster

793. Spatial and Feature-Based Attention

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Topic: D.04. Vision

Support: BMBF Grant 01GQ1005C

DFG Collaborative Research Center 889, Project C04

Title: Feature-based attention to visual motion directions increases response and contrast gain: evidence for tuned normalization

Authors: ***P. SCHWEDHELM**[1,2], B. S. KRISHNA[1], S. TREUE[1,2,3];
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Abstract: Paying attention to a sensory feature improves the perception of that feature and can impair processing of other features. Recent work has shown that a Normalization Model of Attention (NMoA: Reynolds & Heeger, 2009) can account for a wide range of physiological findings and is also consistent with the measured influence of different attentional manipulations on visual performance (Herrmann et al. 2010, 2012). A key prediction of the NMoA is that feature-based attention (e.g. attention to orientation or motion direction) will impact neuronal responses by multiplicative scaling of the responses of neurons tuned to the attended feature (response gain), rather than by increasing the effective sensory input strength of the attended feature (input gain). Under the assumption of an optimal perceptual read-out, an effect on

neuronal responses translates to similar patterns of improvement in behavioral performance; with psychometric functions showing response gain rather than input gain when attention is directed to the task-relevant feature. This prediction has been confirmed by one recent report using attention to orientation (Herrmann et al. 2012). However, using a similar experimental design to measure the effects of feature-based attention to visual motion directions, we observed a different pattern of results. We found that when human subjects are cued to attend to one of two motion directions in a transparent motion display, attentional effects on direction discrimination performance are a combination of input gain and response gain. This contradicts predictions made by the NMoA, especially since we found the effect size of input gain to increase when attention is focused on a narrow range of motion directions compared to when it is directed towards a broader range. In order to account for our observations, we suggest a revision of the assumptions made by the NMoA: Adding a direction-tuned, stimulus-independent, attentional contribution to the normalization pool fully accounts for our pattern of results. This proposed direction-tuned attentional normalization is consistent with the feature-similarity gain model of attention and the attentional modulation in extrastriate cortical area MT, where neuronal responses are enhanced or suppressed by attention to preferred and non-preferred motion directions respectively.

Disclosures: **P. Schwedhelm:** None. **B.S. Krishna:** None. **S. Treue:** None.

Poster

793. Spatial and Feature-Based Attention

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Topic: D.04. Vision

Support: German research foundation grant Nr EXC307

Max Planck Society Germany

Title: Top-down attention de-correlates early visual cortex

Authors: *S. KWON[1,2], M. WATANABE[2], A. BARTELS[1,2];
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Abstract: Attention allows our brain to focus its limited resources on a selected task. It does so by the selective modulation of neuronal activity of task-relevant cortical areas, and by the

simultaneous change of communication between sets of regions. Previous fMRI evidence in the human brain showed selective increases in functional connectivity within visual cortex and between visual with fronto-parietal networks. However, these studies examined relatively brief attention periods that are affected by task-induced signal transients. We designed an experiment involving very long (2 min) trials of attention and rest that would allow us to discard initial transient periods (30 s), and to analyze slow (0.004-0.05Hz) and fast frequency (0.05-0.2Hz) bands of fMRI signals driving connectivity changes. We analyzed functional connectivity between visual regions, the dorsal attention network, and the resting state network. We found that attention increased long-distance connectivity between the dorsal attention network and visual regions and within the resting-state network. It decreased connectivity between resting-state and attention networks, but also between distinct visual regions and within distinct parts of the same visual region (left/right, dorsal/ventral parts). The change in connectivity strength was correlated with hierarchical distance, such that the increase between the dorsal attention network and visual cortex was more pronounced for higher than lower visual regions. Correspondingly, the decrease within visual cortex was the more pronounced the closer the hierarchical proximity was between neighboring regions, and was highest within regions. A frequency-segregated analysis showed that long-distance effects between dorsal attention network and visual regions were mediated by slow and fast fluctuations, whereas only fast fluctuations mediated de-correlation among visual regions. These results may pinpoint two fundamentally distinct effects of attention on connectivity. A long-range facilitation of information flow between distinct networks, and a short-range de-correlation within sensory cortex that may indicate and increase of information and decrease of redundancy.

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Poster

793. Spatial and Feature-Based Attention

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Support: NIH Grant EY022727

Title: Attentional priority signals in human frontoparietal cortex correlate with performance in a feature-based attention task

Authors: ***M. JIGO**, T. LIU;
Dept. of Psychology, Michigan State Univ., East Lansing, MI

Abstract: It is generally accepted that top-down visual attention selects goal-relevant stimuli to facilitate task performance. Hence, fluctuations in endogenous attentional control should influence performance in tasks relying on visual selection. Previous research has implicated a dorsal frontoparietal network, including regions in intraparietal sulcus (IPS) and frontal eye field (FEF), in the maintenance of attentional priority for visual features. However, the relationship between the quality of these neural representations and task performance is not well understood. Using two speed detection tasks in an fMRI experiment, we tested whether the quality of an attentional template, i.e., the neural representation of an attended direction of motion, correlated with task performance. In the first task (attention), subjects were cued to attend to one of two overlapping dot fields, one that rotated in a clockwise (CW) direction and another that rotated in a counter-clockwise (CCW) direction. Subjects were instructed to report the presence or absence of a brief speedup in the cued direction. The magnitude of the speedup was controlled by a staircase that constrained performance at 75% correct. In the second task (baseline), subjects similarly reported the presence or absence of a speedup, but they only viewed a single dot field that rotated in either the CW or CCW direction. Speedup magnitudes were equated between tasks. The patterns of neural activity for correct and incorrect trials in each motion direction in the attention task were obtained as the measure of the attentional templates. To get a measure of their respective quality, these templates were compared to the neural patterns obtained from the baseline task, which served as the benchmark template. We found that the attentional templates in posterior IPS and FEF were more similar to the benchmark template for correct than incorrect trials. These effects were not found in visual areas and inferior prefrontal areas. Furthermore, for average fMRI response across voxels, we found a slightly smaller amplitude and temporally more extended profile for incorrect than correct trials in these areas, as well as anterior IPS and inferior prefrontal areas. These results revealed neural correlates of task performance for feature-based attention and suggest that posterior IPS and FEF maintain attentional templates that facilitate the successful selection of relevant visual features.

Disclosures: **M. Jigo:** None. **T. Liu:** None.

Poster

793. Spatial and Feature-Based Attention

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Topic: D.04. Vision

Support: NWO Veni 863.11.020

Title: Parietal theta burst TMS: functional fractionation observed during bistable perception not evident in attention tasks

Authors: *J. BRASCAMP[1,2], G. SCHAUER[3], R. KANAI[3];
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Abstract: When visual input is ambiguous or inconclusive, perception spontaneously alternates between interpretations: bistable perception. The idea that these perceptual alternations are related to attention function has a long history, but arguably the most compelling evidence comes from recent studies using transcranial magnetic stimulation (TMS). These studies have identified two distinct sites near the right intraparietal sulcus (IPS) where offline TMS affects the frequency of occurrence of these alternations, but strikingly with opposite directions of effect for the two sites. Although this clearly implicates right parietal cortex in bistable perception, the functional nature of this involvement remains unclear. It is natural to suppose a link to attention-related functions, as numerous lesions studies, as well as TMS work, have indicated the right parietal cortex in tasks involving functions like attention to spatial locations and sustained attention. Here we use this knowledge in an attempt to functionally interpret right-parietal involvement in bistable perception. Specifically, we used the exact theta burst TMS protocol that we previously used to affect perception of ambiguous stimuli, yet measured its effect on tasks involving attention to lateralized targets and sustained attention. Although there was a trend for TMS to affect these tasks, trends were consistently similar for both parietal sites, with no indication of opposite effects as had been found for perception. We interpret this as signifying that the previously observed parietal fractionation of function regarding the perception of ambiguous stimuli, is not due to TMS-induced modification of spatial or sustained attention.

Disclosures: **J. Brascamp:** None. **G. Schauer:** None. **R. Kanai:** None.

Poster

793. Spatial and Feature-Based Attention

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Topic: D.04. Vision

Support: Deutsche Forschungsgemeinschaft (SFB779/TPA1)

Title: The impact of spatial focusing on global feature-based attention

Authors: *M. V. BARTSCH[1], H. STRUMPF[2], M. A. SCHOENFELD[1,2], J.-M. HOPF[1,2]; [1]Leibniz Inst. for Neurobio., Magdeburg, Germany; [2]Dept. of Neurol., Otto von Guericke Univ., Magdeburg, Germany

Abstract: Attention to features operates in a location-unbound manner, which is referred to as global feature-based attention (GFBA). GFBA is typically revealed by assessing the brain response to task-irrelevant feature probes outside the spatial focus of attention (FOA) as a function of probe-to-target feature similarity (unattended probe paradigm). While this experimental approach yields consistent effects of GFBA, it has some disadvantages. The most important one pertains to the fact that the allocation of spatial attention needs to be carefully controlled, which may be hard to accomplish in particular in experimental designs using onset stimulation. For example, with stimulus onset the spatial FOA may transiently widen and encompass both the target and the probe - a situation that would confound GFBA with transient effects of spatial selection. Here, we address this issue in a series of magnetoencephalographic (MEG) experiments in human observers performing a color attention task by manipulating the allocation of spatial attention to the color target in three different ways: (1) We motivate stronger spatial focusing by increasing the difficulty of discriminating the color target. (2) We facilitate more consistent focusing by demarcating the target location with placeholders prior to stimulus onset. (3) We aid optimal spatial focusing by presenting the target at fixation. We observe that all three manipulations leave the spatiotemporal pattern of modulations underlying global color-based attention largely unchanged. The pattern appears as a series of modulations of the neuromagnetic response in ventral extrastriate cortex contralateral to the probe, which was previously documented in Bartsch et al. (2014). These results together suggest that the GFBA response as revealed by the unattended probe paradigm indexes a true global selection effect that is not simply arising from inconsistent spatial focusing.

Disclosures: M.V. Bartsch: None. **H. Strumpf:** None. **M.A. Schoenfeld:** None. **J. Hopf:** None.

Poster

793. Spatial and Feature-Based Attention

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Support: Canadian Institutes of Health Research

Natural Sciences and Engineering Research Council of Canada

Title: Attention and normalization responses of area 8a of the primate dorsolateral prefrontal cortex are cell type dependent

Authors: *L. DUONG[1], F. PIEPER[2], J. MARTINEZ-TRUJILLO[3];
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Abstract: It has been proposed that attention modulates the responses of neurons in early visual cortex of primates by regulating the strength of normalization mechanisms. However, whether a similar argument applies to executive areas such as the prefrontal cortex, where attentional modulation of neuronal responses is particularly strong, remains unclear. Here we recorded the responses of neurons in area 8A of the dorsolateral prefrontal cortex of two non-human primates during a task that required the animals to fixate on a central point on a computer screen while being presented with one stimulus presented in one of four quadrants of the visual field, or four stimuli presented simultaneously (one in each quadrant). When multiple stimuli were presented, the animals were cued to attend to one of the four quadrants while holding fixation on the center of the screen. We found that in general, the neuronal firing rates to the four stimuli presented together differed greatly from the sum of firing rates for when they were presented alone, consistent with previously described normalization processes in other areas of the brain. Further, the extent of a neuron's firing rate suppression during single stimulus presentation was related to its firing rate during multiple stimulus presentation. With four stimuli in the visual field, computations resembled an averaging response under conditions with no attention; interestingly however, when attention was directed to one of the stimuli, the response of a subset of contralateral selective cells more closely resembled a winner-take-all computation. Correlational analysis reveals that neurons selective for the ipsilateral or contralateral hemifield may indeed be governed by different underlying circuitry.

Disclosures: L. Duong: None. **F. Pieper:** None. **J. Martinez-Trujillo:** None.

Poster

794. Sensorimotor Transformation: Behavior and Whole Animal

Location: Hall A

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Topic: D.05. Visual Sensory-motor Processing

Support: NIH grant DP1 NS082121-02

Title: Clues about the neuronal basis of UV avoidance in larval zebrafish

Authors: *D. A. GUGGIANA-NILO, F. ENGERT;
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Abstract: Light in the ultraviolet region is invisible to humans, but is ubiquitous in nature as it is one of the components of sunlight. This range of the electromagnetic spectrum is of particular importance to organisms in contact with it, given its higher energy per photon and concomitant potential to generate cellular damage and trigger mutations in DNA. The ability to detect these low wavelengths is present in a variety of organisms, ranging from mammals to insects. One of such organisms is the larval zebrafish (Danio rerio). This small teleost possesses 4 types of cone photoreceptors that can detect wavelengths from the red to the UV and are active as early as 4 days post fertilization (dpf). Additionally, this organism is a newly encumbered model for a variety of fields in biology such as development, pharmacology and neuroscience. This is due to a combination of well-described genetics, rich behavioral and physiological repertoire and optical transparency. In the past we have shown that larvae avoid UV light in an intensity dependent manner and that UV light is able to overcome phototactic behavior. For this we utilized a closed loop paradigm where the fish is tracked as it swims freely in an arena and a projection follows it in real time, forcing a choice of turning direction between 2 different visual stimuli, presented separately to each eye. Given the visual range of the animal, we modified an existing DLP projector to present stimuli fitting the absorption region of the zebrafish and we synthesized color-isolating stimuli to probe each channel separately. In this work we show how mutant larvae with genetically inactivated UV cones fail to avoid UV light, while their wild type siblings show the expected avoidance behavior.

Disclosures: **D.A. Guggiana-Nilo:** None. **F. Engert:** None.

Poster

794. Sensorimotor Transformation: Behavior and Whole Animal

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Topic: D.05. Visual Sensory-motor Processing

Support: Marie Curie

Title: Relating individual variability of behavior and neural circuitry in the optomotor response of larval zebrafish

Authors: *E. A. NAUMANN[1,2], T. W. DUNN[1], J. E. FITZGERALD[1], J. RIHEL[2], F. ENGERT[1];
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Abstract: How are individual behavioral differences manifested in underlying neural circuits? In order to study the heterogeneity of a basic vertebrate visuomotor neural circuit, we performed a detailed kinematic analysis of behavioral signatures across individual zebrafish swimming in response to monocular and binocular optic flow stimuli. Using a closed-loop assay to control the visual environment precisely while monitoring behavior, we quantified kinematic variability across individual fish. While each fish effectively matches its behavior to the speed and direction of visual motion, we find that the exact behavioral implementation varies substantially across individuals. To correlate fish-specific behavioral idiosyncrasies with neural circuit activity, we used whole-brain calcium imaging to examine functional differences across the same individuals subjected to behavioral assays. Our results show that individual differences in cumulative angle changes and binocular integration correlate the distribution of specific neural response classes in the pretectum, a brain region primarily involved in optic flow processing. These correlations parameterize model families that generate predictions for circuit composition and connectivity strength between functional cell types. Together with anatomical tracing of neural projection patterns and assessments of neurotransmitter identity, these experiments establish a theoretical minimal neural circuit and illustrate the degree to which circuit architecture is degenerate across individuals. This study of circuit heterogeneity across individuals is crucial for our understanding functional degeneracy within neural circuits and suggests limitations for standard models fit on average data.

Disclosures: E.A. Naumann: None. **T.W. Dunn:** None. **J.E. Fitzgerald:** None. **J. Rihel:** None. **F. Engert:** None.

Poster

794. Sensorimotor Transformation: Behavior and Whole Animal

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Topic: D.05. Visual Sensory-motor Processing

Title: Experience shapes prey capture behavior and neural representations in larval zebrafish

Authors: *C. OLDFIELD[1], E. CARROLL[2], M. CHAVEZ[3], C. WYART[4], E. ISACOFF[2];
[1]Isacoff lab - MCB, UC Berkeley, Berkeley, ; [2]Isacoff lab - MCB, UC Berkeley, Berkeley, CA; [3]ICM - UPMC, Paris, France; [4]ICM, Paris, France

Abstract: When larval zebrafish first open their mouths and start hunting for prey during their fifth day post-fertilization (5 dpf), they may have seen edible organisms before, but without ever eating. Despite this lack of experience, they capture prey, such as paramecia, in a highly stereotyped manner. Prey is detected visually, the fish then reorients its body precisely towards the prey and darts forward to engulf the prey in a final capture swim. Recent work has dissected the visual circuits that lead to prey capture, but how information is transmitted to motor centers is unclear. Using a combination of behavioral assays and whole brain calcium imaging, we are working to understand the relationship between experience-based changes in brain activity and prey capture behavior.

Disclosures: C. Oldfield: None. **E. Carroll:** None. **M. Chavez:** None. **C. Wyart:** None. **E. Isacoff:** None.

Poster

794. Sensorimotor Transformation: Behavior and Whole Animal

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Program#/Poster#: 794.04/N41

Topic: D.05. Visual Sensory-motor Processing

Title: Light-evoked diving reflex in zebrafish larvae

Authors: B. H. BISHOP, B. C. FRESHNER, *E. B. GAHTAN;
Psychology, Humboldt State Univ., Arcata, CA

Abstract: Escape behaviors have been studied in many organisms by neuroscientists seeking detailed, cellular- and synaptic-level descriptions of functional circuits. Escapes are useful because they can be elicited repeatedly and have consistent kinematics. Analysis of escape circuits in fish have revealed mechanisms for movements away from a threatening stimulus (contraversive) in the lateral plane, such as commissural projections and population coding of escape turn angle. However, while most fish navigate in 3 spatial dimensions, few studies have examined neural mechanisms of vertical movements during escape. We characterized vertical escape swimming in zebrafish larvae using synchronized imaging from two cameras viewing a 10cm3 tank. Escapes elicited by dimming of ambient light consistently elicited downward spiral swimming (dives). At 20s post dimming, larvae showed more vertical (-18.8±2mm) than horizontal (3.2±0.6mm) displacement. The average slope of dives was -1.9±.35, meaning larvae move about twice as fast vertically than horizontally along their spiral paths. In a tubular tank with more vertical (400mm) than horizontal (100mm) range, vertical movement 120s after light dimming was -353±8.39mm (~70 body lengths downward). Dives typically began within 1s after

light dimming and continued until the tank bottom was reached. Maximum descent rate was 10.75mm/s (at 58s post dimming), and average descent rate was 5.41±0.24mm/s. Auditory taps also elicited rapid escape swimming with equivalent total distance traveled 20s post stimulus but with significantly less vertical and more horizontal displacement than on dimming-evoked escapes. These results suggest that light dimming-evoked spiral diving in larval zebrafish may be a protean escape reflex to specific types of predation threats, and that neural circuit models of escape control must look beyond mechanisms for lateral contraversive movements and also consider vertical movement control elements.

Disclosures: **B.H. Bishop:** None. **B.C. Freshner:** None. **E.B. Gahtan:** None.

Poster

794. Sensorimotor Transformation: Behavior and Whole Animal

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Topic: D.05. Visual Sensory-motor Processing

Support: Howard Hughes Medical Institute

Title: A novel neuromodulatory circuit for short-term motor memory

Authors: *T. KAWASHIMA, C.-T. YANG, M. B. AHRENS;
HHMI Janelia Res. Campus, Ashburn, VA

Abstract: Animals continually adapt to the dynamics of environmental feedback arising from behavior. Here we report on the discovery of a novel neural substrate of a short-term memory of adapted behavioral states mediated by the dorsal raphe nucleus, a neuromodulatory serotonergic nucleus in vertebrates. When larval zebrafish perform adaptive motor control within the optomotor response (OMR), extended exposure to a given feedback gain - the strength of visual feedback driven by fictive swimming - establishes a short-term memory of the matched locomotor drive, which is maintained for periods of up to 20 seconds of behavioral inactivity. We used light-sheet microscopy to perform whole-brain calcium imaging in larval zebrafish behaving in virtual reality to identify neural circuits underlying this short-term motor memory. Functional brain maps identified the dorsal raphe nucleus (DRN) as a key regulatory region for the memory of attenuated locomotor drive resulting from high feedback gain. Activity of DRN neurons built up during low locomotor drive, was maintained during periods of behavioral inactivity, and was predictive of the subsequent motor output, indicating that DRN activity can support a persistent memory trace of the adapted locomotor state. Spiking responses of DRN

neurons showed a combination of phasic sensorimotor responses and additional modulation of tonic activity. Chemical-genetic lesions of DRN serotonergic populations reduced the ability to form the short-term motor memory; and optogenetic activation of DRN neurons induced lasting depression of locomotor drive similar to the experience-induced attenuation of behavioral vigor. These results uncover a novel mechanism for a short-term motor memory.

Disclosures: **T. Kawashima:** None. **C. Yang:** None. **M.B. Ahrens:** None.

Poster

794. Sensorimotor Transformation: Behavior and Whole Animal

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Title: Sensory cortical control of a visually induced arrest behavior via corticotectal projections

Authors: F. LIANG, X. R. XIONG, B. ZINGG, X.-Y. JI, L. I. ZHANG, *H. TAO;
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Abstract: Innate defense behaviors (IDBs) evoked by threatening sensory stimuli are essential for animal survival. Although subcortical circuits are implicated in IDBs, it remains largely unclear whether sensory cortex modulates IDBs and what are the underlying neural pathways. Here, we show that optogenetic silencing of corticotectal projections from layer 5 (L5) of the mouse primary visual cortex (V1) to the superior colliculus (SC) significantly reduces a SC-dependent innate behavior, i.e. temporary suspension of locomotion upon a sudden flash of light as short as milliseconds. Surprisingly, optogenetic activation of SC-projecting neurons in V1 or their axon terminals in SC sufficiently elicits the behavior, in contrast to other major L5 corticofugal projections. Thus, via the same corticofugal projection, visual cortex not only modulates the light-induced arrest behavior, but also can directly drive the behavior. Our results suggest that sensory cortex may play a previously unrecognized role in the top-down initiation of sensory-motor behaviors.

Disclosures: **F. Liang:** None. **X.R. Xiong:** None. **B. Zingg:** None. **X. Ji:** None. **L.I. Zhang:** None. **H. Tao:** None.

Poster

794. Sensorimotor Transformation: Behavior and Whole Animal

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 794.07/N44

Topic: D.05. Visual Sensory-motor Processing

Support: Emory SIRE Program

Howard Hughes Medical Institute

Title: Visual context and neural control of headbobs in gerbils

Authors: ***H. R. RODMAN**[1], G. KUI[2], K. BANDA[3], M. KRYSIAK[1];
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Abstract: Head bobs are up-down movements, associated with the use of motion parallax for depth perception, that are displayed by many animals, including rodents, birds, and humans. Mongolian gerbils *(Meriones unguiculatus)* show robust visually guided jumping behavior and often execute a series of head bobs prior to jumping. Here, we asked if head bobs are affected by ecologically significant aspects of the visual context, specifically ambient light level and distance to target. In addition, we explored the role of two brain regions - the temporal posterior cortical area (TP) and the superior colliculus (SC) - expected to have important roles in rodents' ability to process visual motion cues. Gerbils were tested on a jumping stand task and head bobs videotaped under three light levels: bright (akin to low daylight; ~1000 lux), dim (akin to dawn or dusk; ~100 lux), and low light (akin to moonlight; ~1 lux), across a range of gap distances (5-45 cm between jumping and target platforms). Infrared illumination was used with a sensitive security camera (Sony SSC-M183). Following euthanasia, cortical flatmounts were prepared, sectioned, and stained for myelin (Gallyas method) to reveal TP, and brainstems were sectioned coronally and stained with cresyl violet. Head bobs were defined as repeated vertical displacements of the head with forepaws resting on the edge of the start platform, facing the landing platform. Head bobs increased with gap distance until an intermediate point and then decreased, suggesting that they are maximally executed under conditions where they are most useful. Significant effects of light level ($p < 0.05$) were found for intermediate distance and intermediate illumination as well as for low illumination and short distances. Thus, the effect of

illuminance on head bobs appears to interact with distance. There was a positive correlation between head bob frequency and relative SC volume, but no overall relationship between head bobs and relative area of the TP region. The results suggest that gerbils use a specific visuomotor strategy for depth perception differentially under different conditions and that the SC is involved in headbob generation and/or use, although further work is needed to investigate potential cortical mechanisms and to pinpoint the role of the SC. The findings are consistent with our earlier work (Krysiak et al., 2011, *Behavioural Processes*) showing that both visuomotor behavior and visual discrimination are modulated by ambient illumination, underscoring the importance of employing ecologically relevant lighting conditions in comparing visual specializations and their neural control across taxa.

Disclosures: **H.R. Rodman:** None. **G. Kui:** None. **K. Banda:** None. **M. Krysiak:** None.

Poster

794. Sensorimotor Transformation: Behavior and Whole Animal

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EU FP7 FET-Open HIVE project 222079

Title: Effects of transcranial direct-current stimulation on the primary visual cortex excitability in alert rabbits

Authors: *J. MARQUEZ-RUIZ[1], C. AMMANN[1], T. COSTA[2], G. LOURENCON[2], I. CORDONES[3], A. GRUART[1], J. DELGADO-GARCÍA[1], D. VENTURA[2];
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Abstract: During the last decades, transcranial direct-current stimulation (tDCS) has demonstrated to be a valuable tool for non-invasive manipulation of cortical excitability. The aim of this study was to investigate the effects of tDCS over the primary visual cortex (V1) of alert rabbits, demonstrating the capability of tDCS to modulate the sensory perception involved in complex cortical processes, such as the acquisition of an associative learning task, as well as the way in which tDCS affects the oscillatory activity of cortical circuits. For this objective four male rabbits were prepared for chronic recording of visual evoked potentials (VEPs) and classical eyeblink conditioning during simultaneous tDCS. To describe excitability changes of V1 after anodal and cathodal tDCS presentation (2 mA, 20 min), VEPs were recorded before and after tDCS in response to visual stimulation induced by trains of flashes (20 flashes, 1 Hz). tDCS stimuli were applied through four silver ball electrodes placed above the skull (targeted active electrode) and a saline-soaked sponge attached to the contralateral ear serving as a counterelectrode. To show whether changes induced by tDCS in V1 excitability modify associative learning in rabbits, a classical eyeblink conditioning was carried out in the animals. Accordingly, we used a trace paradigm presenting a train (100 ms, 50 Hz) of flashes as conditioned stimulus (CS), followed 250 ms later by an air puff (100 ms) as unconditioned stimulus (US). Anodal and cathodal tDCS (2 mA, ~20 min) were applied during conditioning day 2 (C2) and day 8 (C8), respectively. The EMG activity of the orbicularis oculi was used to define the conditioning responses (CRs). The results show a significant long-lasting increase of the P1 amplitude after cathodal stimulation, while anodal stimulation did not induce any change in VEPs. The analysis of the event-related spectral power associated to the VEPs showed that cathodal tDCS on V1 reduces 70-100 Hz and increases 5-40 Hz bands spectral power whereas no changes were observed after anodal tDCS. In addition, the presence of anodal tDCS during C2 did not show any effect on the acquisition of the CRs, while during cathodal stimulation during C8 animals showed a statistically significant lower percentage of CRs with CRs showing lower orbicularis oculi EMG activity and slower latencies. The present work highlights new electrophysiological and behavioural data, obtained for the first time in awake animals, demonstrating the long-lasting modulation effects of cathodal tDCS on V1 excitability, and its consequent modulation of visual perception involved in the performance of an associative learning task.

Disclosures: **J. Marquez-Ruiz:** None. **C. Ammann:** None. **T. Costa:** None. **G. Lourencon:** None. **I. Cordones:** None. **A. Gruart:** None. **J. Delgado-García:** None. **D. Ventura:** None.

Poster

794. Sensorimotor Transformation: Behavior and Whole Animal

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Program#/Poster#: 794.09/N46

Topic: D.05. Visual Sensory-motor Processing

Support: KAKENHI 254300023

Title: Pulvinar inactivation impairs the visually guided saccade in the blindsight monkeys

Authors: ***M. KINOSHITA**[1], R. KATO[2], K. ISA[2], K. KOBAYASHI[3], H. ONOE[4], T. ISA[2]; [1]Hirosaki Univ. Sch. of Med., Hirosaki, Japan; [2]Dept. of Developmental Physiol., [3]Section of Viral Vector Develop., Natl. Inst. for Physiological Sci., Okazaki, Japan; [4]Ctr. for Life Sci. Technologies, RIKEN, Kobe, Japan

Abstract: Damage to the primary visual cortex (V1) causes a loss of visual awareness in the corresponding visual field. Some patients with such cortical scotoma in V1, however, can localize a visual target presented in such blind visual field. This phenomenon is called 'blindsight' and thought to be derived from the function of residual visual pathways bypassing the V1. The critical role of superior colliculus (SC) was indicated by the inactivation of SC in unilateral V1-lesioned monkeys (Mohler and Wurtz 1977; Kato et al., 2011). It has been proposed that the pulvinar nucleus, which receives input from SC and sends information to higher visual cortical areas, relay the visual signal for the blindsight. However, a recent study proposed that the lateral geniculate nucleus, instead of the pulvinar, is essential for the blindsight (Schmid et al., 2010). In this study, we have tested the role of the ventrolateral part of pulvinar nucleus (vlPul) for the visually guided saccade (VGS) task in the unilateral V1-lesioned monkeys. We trained two unilateral V1-lesioned macaque monkeys to perform a VGS to the target presented in the blind visual field corresponding to the lesioned V1. To identify the location of vlPul, we made electrophysiological recordings in the pulvinar and sought for the sites which contained neurons with mono- or oligo-synaptic responses to the electrical stimulation of the SC. Subsequently, we made micro-injections of muscimol (0.2-0.5 µl, 0.5 µg/µl) into the vlPul. The correct ratio of the VGS task in the blind field was significantly decreased and saccadic reaction times were prolonged after the injection. This result suggests that the vlPul plays a critical role for the blindsight. The pulvinar receives input not only from SC but also from other areas. Therefore, the next question was whether the SC-vlPul pathway was important for the blindsight. To answer this question, we tested the VGS performances after the selective blockade (Kinoshita et al., 2012) of the SC-vlPul pathway. We injected the retrograde viral vector carrying tetanus neurotoxin gene (FuGB2-TRE-eTeNT.GFP) into the vlPul and injected the anterograde vector (AAV1-CMV-rtTAV16) into the SC. Several weeks after these injections, only neurons with cell bodies at SC and projection to the vlPul expressed the tetanus neurotoxin, which blocks their synaptic transmission, under the administration of doxycycline. Several days after start of the doxycycline administration, we found the impairment of VGS performance in the blind field. These results suggest that the vlPul plays a critical role for the blindsight and that the SC-vlPul pathway mediates the visual signal.

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Poster

794. Sensorimotor Transformation: Behavior and Whole Animal

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Topic: D.05. Visual Sensory-motor Processing

Support: NIH grant EY03878

Howard Hughes Medical Institute

Title: Bayesian priors created by single trials in smooth pursuit eye movements

Authors: ***T. DARLINGTON**[1], S. LISBERGER[2];
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Abstract: Many behaviors operate in a Bayesian framework, where actions are guided by a complex interaction between current sensory information and past experience, or "priors". When current sensory information is weak, it is advantageous to allow the prior to guide behavior. However, the value of prior experience lessens as sensory information strengthens. A previous publication from our lab has shown that several days of experience can create a prior for estimates of target direction to drive pursuit eye movements. We now show that priors can be modified on a trial-by-trial basis. Two male rhesus macaque monkeys were trained to track a 100% contrast patch of dots (strong sensory stimulus) and a 12% contrast sine wave grating (weak sensory stimulus) with smooth pursuit eye movements. In one set of experiments, we found that pursuit direction on a "test" trial was biased toward the target direction of the "prior" trial. The effect of the prior appeared when the direction difference between two trials was 15, 45, or 90 degrees and was largest when the difference was 45 degrees. The prior was expressed more strongly on test trials that used the weak motion provided by low-contrast gratings. The directional bias continued to grow during the steady-state phase of pursuit for grating targets, but was suppressed after the initiation of pursuit for patch targets. In a second set of experiments, we found that the magnitude of expression of the prior on a "test" trial increased as the number of identical "prior" trials increased from 1 to 10. We conclude that smooth pursuit is able to operate under a Bayesian-like framework on the scale of single trials.

Disclosures: **T. Darlington:** None. **S. Lisberger:** None.

Poster

794. Sensorimotor Transformation: Behavior and Whole Animal

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: D.05. Visual Sensory-motor Processing

Support: CNPq - Brazil

Title: Congruency effect for objects and grips based on predictiveness

Authors: ***R. P. LIMA**[1], C. HEYES[2], G. W. HUMPHREYS[3];
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Abstract: xxx

Disclosures: **R.P. Lima:** None. **C. Heyes:** None. **G.W. Humphreys:** None.

Poster

794. Sensorimotor Transformation: Behavior and Whole Animal

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Topic: D.05. Visual Sensory-motor Processing

Support: NSERC (Canada)

ORF (Canada)

CFI (Canada)

Title: Neck muscle sensory noise alters visual-proprioceptive integration weights due to stochastic reference frame transformations

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Abstract: During reaching, humans combine visual and proprioceptive information in a statistically optimal manner (Multi-Sensory Integration, MSI). To do so, the weak fusion model stipulates that these signals should undergo a reference frame transformations (RFT) into a common frame before integration. A previous study (Burns & Blohm, 2010) observed that introducing Head Roll (HR) increased the variability in Reach Errors (REs) and speculated that signal-dependent noise (SDN) in HR estimation adds variability to the transformed signals and thus affects their MSI weights. An alternative interpretation is that MSI weights change due to uncommon head roll postures instead of added noise in RFTs. To distinguish between these alternatives, we set out to modulate neck muscle sensory noise by loading the head. Participants stood in front of a virtual reality robotic setup (KINARM, BKIN Technologies) and performed center-out reaches toward one of eight visual targets uniformly distributed on a 10cm radius circle, while keeping their gaze at the center. A conflict between visual and proprioceptive information occurred by shifting the hand 2.5cm either vertically or laterally while providing visual feedback showing initial hand position at the center. The task was with 3 HR rotations; 0 and ±30 degrees and 3 Neck Load (NL) conditions (1.8kg simulating neck muscle tension at 30deg HR; leftward/rightward and no load) for each HR. We hypothesized that altering neck muscle force will create different levels of SDN in HR estimation, which should result in more variability in RFTs ultimately affecting the weights of MSI and reaching pattern. For 0 deg HR, we found that REs in the control condition (no NL and no HR) fell between REs observed when applying NL, with significant shifts in RE curves (ANOVA: $F(44,2) = 8.29$, $p=0.0004$). In addition, the variability in RE in trials with NL was higher than during controls. We also found increase in variability by changing HR at no NL conditions, consistent with Burns & Blohm (2010). However, we found higher variability in REs for changing HR (@ NL = 0) compared to changing NL (@ HR = 0). This increase in variability by increasing the HR estimation suggests that SDN in the internal estimate of HR induces variability into the RFT. As a result, MSI weights decreased for transformed signals when applying either HR (NL=0) or NL (HR = 0) with a higher decrease for changing HR. Together, these results confirm that RFTs should indeed be regarded as stochastic in nature and that previous results cannot be explained by unfamiliar postures. It also shows that noise in muscle spindles has an observable effect on reference frame transformations underlying reach planning.

Disclosures: P. Abedi Khoozani: None. **G. Blohm:** None.

Poster

794. Sensorimotor Transformation: Behavior and Whole Animal

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Program#/Poster#: 794.13/O2

Topic: D.05. Visual Sensory-motor Processing

Support: Grain-in-Aid for Young Scientists (B)

Title: Learning time-to-contact in ball catching without haptic information

Authors: ***H. KAMBARA**, N. HAMA, T. KAWASE, N. YOSHIMURA, Y. KOIKE;
Tokyo Inst. Technol., Yokohama, Japan

Abstract: A successful catch of a falling ball requires an accurate estimation of Time-to-Contact (TTC), that is, the time remains before the ball hits the hand. In a series of past experiments, human subjects exhibited the ability to catch a ball in a virtual reality environment where the virtual ball fell with several different accelerations. Since our visual system is poor in detecting exact acceleration of moving objects, some kind of information about its acceleration must be learned and used as the prior knowledge in TTC prediction. In this study, we hypothesize that human can modify internal model of the acceleration of the freely falling ball according to the error between expected and actual hand motion before and after catching the ball. To verify this hypothesis, we conducted ball-catching experiments in a virtual reality environment, which allowed participants to recognize the ball contact to the hand by visual information only. Our results indicated that three out of four participants could learn another acceleration other than the gravitational acceleration by visual information.

Disclosures: H. Kambara: None. **N. Hama:** None. **T. Kawase:** None. **N. Yoshimura:** None. **Y. Koike:** None.

Poster

794. Sensorimotor Transformation: Behavior and Whole Animal

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Topic: D.05. Visual Sensory-motor Processing

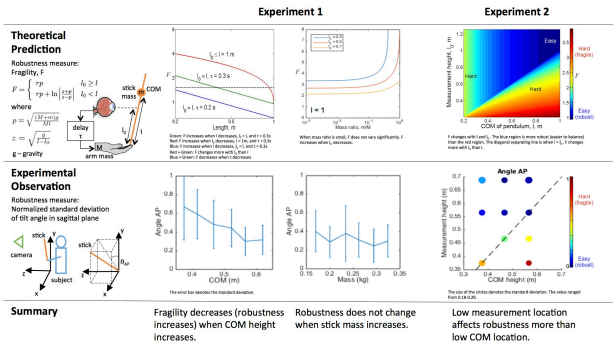
Support: U.S. Army Research Office Grant W911NF-09-0001

NIH BRP Grant #1R01 EB007615

Title: The significance of measurement location in human stick balancing

Authors: Y. LEONG[1], B. CHRISTALIN[1], *J. W. BURDICK[2], J. C. DOYLE[1];
[1]Control & Dynamical Systems, [2]Caltech, Pasadena, CA

Abstract: Human stick balancing has been extensively studied as a simple case study of human sensorimotor control. Multiple control frameworks were proposed to explain experimentally observed dependencies in delay, noise, and stick center of mass (COM). The goal of this research is to merge these seemingly independent observations into a single consistent framework - robust control theory. It provides a fundamental limit on the robustness (ability to balance) of a feedback control system (stick balancing) independent of the controller details (nervous system). Analytical analysis shows that: a) feedback delay reduces robustness, b) lower COM is harder to balance, c) measurement location (the point where the eyes focus on a stick) below the COM is extremely hard to balance, and d) stick mass has minimal effects on robustness. Inspired by the analytical results, the effects of COM location (L), measurement location (L_0), and stick mass (M_s) in balance performance are studied experimentally. Twelve healthy adult subjects (23 - 29 y/o) engaged in 2 sets of experiments. The first set (5 subjects) studies the influence of M_s and L, and the second set (7 subjects) studies the influence of L and L_0. In each trial, a subject balances a stick while looking at a specific location on the stick until the stick falls or the balancing time reaches 1 min. Subjects wear a cap to limit peripheral vision above L_0. The stick and subject's head motion are tracked using OptiTrack. The ability to balance is quantified using standard deviation of stick tilt angle, mean speed of the COM, and length of balancing time. Below, the term "hard to balance" implies these quantities are large. The major finding of these experiments (see figure) is that small L_0 = L is hard (consistent with previous work), but L_0 < L is dramatically harder, an effect never considered in previous studies. Apart from this main result, consistent with analytical predictions, we find that changing M_s has minimal effect. Lastly, the stick most frequently falls in the sagittal plane, implying that the stick motion in sagittal plane is hard.



Disclosures: **Y. Leong:** None. **B. Christalin:** None. **J.W. Burdick:** None. **J.C. Doyle:** None.

Poster

795. Visually Guided Reaching and Eye Movements

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Topic: D.05. Visual Sensory-motor Processing

Support: Landesgraduiertenförderung

DFG Ka 1258/10-1

Title: Auditory and proprioceptive reaching in a patient with optic ataxia

Authors: *S. CORNELSEN[1], M. HIMMELBACH[2];
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Abstract: Patients with optic ataxia show deficits in reaching movements to visual targets in the peripheral visual field. Even though the very name optic ataxia suggests an isolated deficit in visuomotor coordination, there is some evidence that the disorder is not restricted to visual targets, but also affects reaching to proprioceptive and auditory targets. These findings suggest that optic ataxia is a multimodal deficit. However, similar proprioceptive misreaching can also be observed in the absence of optic ataxia. In their seminal group study Perenin and Vighetto (1988) excluded any auditory misreaching but reported only qualitative observations without any quantitative data. Taken together, there is conflicting evidence for a new interpretation of optic ataxia as a multimodal ataxia. We investigated a chronic patient (IT) with optic ataxia and visual hemiagnosia in reaching tasks with visual, auditory and proprioceptive targets, for the first time directly comparing all three modalities. Our results replicated the characteristic pattern of visual misreaching in optic ataxia patients: IT was comparable with age-matched healthy controls when reaching to foveated visual targets, but her end-point accuracy decreased for peripheral targets in the contralesional hemifield with larger errors for her contralesional hand than for her ipsilesional hand. This visual misreaching was dissociated from auditory-guided reaching since IT's movements to auditory targets revealed no deficits in comparison to healthy controls. Her movements to proprioceptive targets and movement errors were influenced by the amount and kind of visual feedback with different error patterns with closed eyes in comparison to open eyes with and without fixation during movement execution. We conclude that spatial errors consistent with optic ataxia can co-occur in other modalities, but the disorder is not necessarily multimodal in nature.

Disclosures: S. Cornelsen: None. **M. Himmelbach:** None.

Poster

795. Visually Guided Reaching and Eye Movements

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Program#/Poster#: 795.02/O5

Topic: D.05. Visual Sensory-motor Processing

Support: NSERC

FRQ-S

Title: Selective attenuation of visual reafferent signals in parietal cortex during movement

Authors: *P.-M. BERNIER[1], M. BÉNAZET[1], F. THÉNAULT[1], K. WHITTINGSTALL[2]; [1]Dept. de Kinanthropologie, [2]Radiologie diagnostique, Univ. De Sherbrooke, Sherbrooke, QC, Canada

Abstract: Cortical processing of sensory information is modulated by descending motor commands. For instance, proprioceptive signals from one's moving limb are attenuated in secondary somatosensory areas during voluntary movement (Blakemore, Wolpert, & Frith, 1998). Similarly, auditory signals are attenuated in primary auditory cortex when self-initiated (Baess et al., 2009; Horvàth, 2015). Strikingly, this phenomenon has not been investigated in the visual domain. In particular, it is unknown whether reafferent visual signals from one's moving limb are also attenuated at the cortical level during voluntary movement. Here we address this issue by recording electroencephalography and measuring the visual evoked potentials (VEPs) elicited by visual feedback of the hand in motion. Nineteen subjects had to move their right hand to a target located 20 cm straight ahead in ~800ms. We manipulated the temporal relationship between hand visual feedback (represented via a cursor) and actual hand motion. In the real-time condition, subjects were shown their hand visual feedback with 0ms lag. In the delayed condition, they were shown their hand visual feedback with a 150ms lag. Critically, the spatial properties of the visual feedback being provided was identical in both conditions. We hypothesized that VEPs would be attenuated in the real-time condition as compared to the delayed condition. We focussed on the VEPs in parietal and premotor regions, which are known to receive and process visual information (Tanne-Gariepy et al. 2002; Grefkes & Fink, 2005; Theys et al., 2013). We report two main findings. First, in line with our hypothesis, we found a significant attenuation of the N1 component at bilateral parietal electrodes (P1, CP1, P2, CP2) in the real-time condition as compared to the delayed condition, peaking 160 ms after presentation of visual feedback ($p < 0.05$). Second, we observed the reverse modulation in the left premotor electrodes (C3, FC3). Specifically, VEP amplitude was significantly facilitated in the real-time

condition as compared to the delayed condition, peaking 140 ms after presentation of visual feedback ($p < 0.01$). These results demonstrate that reafferent visual signals from one's moving limb are attenuated during voluntary movement. However this effect is selective to parietal areas at a relatively late stage of visual processing (~160ms). The modulation in parietal responsiveness to visual stimuli may be linked the implication of parietal regions in integrating sensory modalities such as vision and proprioception during reaching (Andersen et al., 1997; Baumann et al., 2009).

Disclosures: **P. Bernier:** None. **M. Bénazet:** None. **F. Thénault:** None. **K. Whittingstall:** None.

Poster

795. Visually Guided Reaching and Eye Movements

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Topic: D.05. Visual Sensory-motor Processing

Support: NSERC Discovery Grant to L Sergio

Title: Video games and visuomotor-related brain activity in women

Authors: *D. J. GORBET[1], L. E. SERGIO[2];
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Abstract: Action video games are fast-paced games requiring quick reactions and focused attention. The scientific literature is beginning to accumulate a lot of convincing evidence that a history of playing action video games is associated with enhancements to some forms of visual perception and attention relative to individuals who do not play these types of games. These findings make action video games an increasingly attractive possibility for creating visuomotor neurorehabilitation approaches that are both effective and enjoyable. Indeed the use of video games for neural rehabilitation has become increasingly common in clinical settings. However, in the current literature, studies of the effects of long-term action video game play focus almost exclusively on male participants. Given that there are known sex-related differences in the functional brain networks involved in visuomotor control, it is important to gain an understanding of the potential effects of video game play in women in addition to men in order to design games that can be used as effective rehabilitative tools. In the study presented here, we used fMRI to examine visuomotor-related brain activity in women who have played action video

games for a minimum of 10 hours a week for at least the last 3 years. Preliminary results suggest that relative to women who play little or no video games, action video game play is associated with decreased activity in the left medial parietal-occipital cortex and bilaterally in the superior posterior cerebellum. These results shed light on the neural correlates of action video game play in women. Importantly, these results differ somewhat from what we have previously observed in men (Granek et al., 2010), suggesting that it will be necessary to examine potential sex-related differences in the effects of video game-induced neural plasticity. Granek, J.A., Gorbet, D.J., Sergio, L.E. (2010) Cortex 46: 1165-1177.

Disclosures: **D.J. Gorbet:** None. **L.E. Sergio:** None.

Poster

795. Visually Guided Reaching and Eye Movements

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Topic: D.05. Visual Sensory-motor Processing

Support: IRTG 1901 "The brain in action" (DFG)

Title: Virtual breakfast: reference frames for goal-directed reaching in a 3D virtual reality environment

Authors: ***I. SCHUETZ**, M. KLINGHAMMER, K. FIEHLER;
Justus-Liebig-University Giessen, Giessen, Germany

Abstract: When reaching for an object such as a coffee mug on a desk, humans are able to integrate egocentric (i.e., relative to themselves) and allocentric spatial information (i.e., relative to other objects in the visual scene). So far, these processes have mostly been studied using abstract stimuli such as LEDs or simple shapes, limiting the possibility to generalize these findings to more natural situations. Using naturalistic photographs of a breakfast table, a previous report from our lab has shown that a change in surrounding objects (i.e., landmarks) influences reaches towards a target object in the scene (Fiehler et. al, 2014). The present experiment aims to further increase the ecological validity of this paradigm by presenting a visual scene in a 3D virtual reality (VR) environment instead on a 2D monitor. Second, we aimed to extend our previous findings to the integration of egocentric and allocentric information in depth. We presented a breakfast scene with six possible goal objects stereoscopically using an Oculus Rift DK2 head mounted display (HMD). To control for correct fixation, eye movements were recorded in VR using an eye tracker installed in the HMD. Participants freely explored the

scene visually, which then disappeared following a button press. After a mask image and subsequent delay, the scene reappeared with one object missing (= reach target) and the others shifted on the table surface either horizontally (left- or rightwards) or shifted in depth (forward or backward). Participants indicated the remembered target location by reaching to the corresponding position on the table in front of them with their right index finger. Finger position was measured using Optotrak and a cursor indicating the current finger position was always visible in the VR environment. We then compared actual reach endpoints in the object shift conditions to the baseline condition in which no object shifts occurred. We found that horizontal reach endpoints were systematically shifted in the predicted direction, i.e. right when the landmarks were moved rightwards and vice versa. In the horizontal direction, the size of the effect was comparable to our previous studies using 2D images. Moving the landmarks in depth also produced systematic reach errors, but effects were more variable across participants. Our results confirm that humans combine egocentric target information with allocentric information from surrounding objects when performing memory-guided reaching movements in a naturalistic 3D scene. This study also highlights the use of VR in action research.

Disclosures: I. Schuetz: None. **M. Klinghammer:** None. **K. Fiehler:** None.

Poster

795. Visually Guided Reaching and Eye Movements

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 795.05/O8

Topic: D.05. Visual Sensory-motor Processing

Support: MIUR

FIRB2013 n° RBFR132BKP

Title: Prevalence of hybrid body-hand reference frames for reaching in area PEc

Authors: V. PISERCHIA[1], R. BREVEGLIERI[1], K. HADJIDIMITRAKIS[2,1], F. BERTOZZI[1], C. GALLETTI[1], *P. FATTORI[1];
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Abstract: A debated topic of research in neuroscience is that of reference frame transformations. The neural processes that underlie these transformations occur mainly in the posterior parietal cortex (PPC). In the medial part of PPC, targets are represented in body- centered and mixed body/hand-centered frame of reference caudally (area V6A), and in hand-centered frame of

reference rostrally (area PE). Here, we assessed the reference frames of neurons in area PEc, located between V6A and PE, during the planning (PLAN) and execution (REACH) of arm reaching movements. We examined the activity of 104 single cells recorded in three Macaca fascicularis. The animals performed in darkness a foveal reaching towards targets located at different depths and in different directions. The reaches could start from two different hand positions, one close to the body and the other far from it, at a different depth. We show that most neurons (80% during PLAN and 65% during REACH) encode targets in a mixed body/hand-centered reference frame. Some (15% during PLAN and 28% during REACH) body-centered cells were present, while a marked absence (5% during PLAN and 7% during REACH) of hand-centered coding was found in both epochs. Present results demonstrate that in PEc there is an intermediate coding between body and hand coordinates in the large majority of the cells. Compared with our recent findings in V6A, under identical task conditions, the effect of initial hand position was stronger in PEc. In summary, the functional properties of PEc suggest that it represents an intermediate node -between V6A and PE- in the gradual transformation of reference frames in the medial PPC.

Disclosures: **V. Piserchia:** None. **R. Breveglieri:** None. **K. Hadjidimitrakis:** None. **F. Bertozzi:** None. **C. Galletti:** None. **P. Fattori:** None.

Poster

795. Visually Guided Reaching and Eye Movements

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 795.06/O9

Topic: D.05. Visual Sensory-motor Processing

Support: IU SPH Faculty Research Grant Program

Title: Effect of visuo-proprioceptive realignment on motor cortex excitability

Authors: *F. MUNOZ[1,2,3], A. K. LYNCH[4], H. J. BLOCK[4,2];
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Abstract: There is a strong relationship between sensory and motor functions: sensory information guides our actions, while our actions typically have sensory consequences. Previous research has shown that active motor learning generates somatosensory changes as measured by sensed limb position. In contrast, passive movements do not show a comparable effect (Ostry et al., 2010). Here we focus on the reverse question: do changes in sensed limb position affect

motor areas of the brain? Transcranial magnetic stimulation (TMS) was used to assess motor cortex physiology before and after participants performed a reaching task. Each participant took part in two sessions: one where visuo-proprioceptive spatial realignment was expected to happen during the reaching task, and another that served as a sham reaching task. Specifically, a recruitment (I/O) curve for the motor cortex representation of first dorsal interosseous (FDI) in the left hand was computed. Motor evoked potentials (MEPs) were recorded for TMS intensities ranging from 90%-130% of the intensity necessary to produce a 1 mV response (SI1mV). For the reaching task, subjects pointed with their right finger to visual (white square), proprioceptive (left index finger), and combined targets with no vision of either hand. In the "real" session, the visual target gradually shifted away from the proprioceptive target so that without subjects noticing, the white square was eventually displayed 70 mm ahead of the left index finger. We have shown previously that this misalignment causes subjects to realign vision, proprioception, or both (Block & Bastian, 2011). In the "sham" session, the white square remained directly over the left index finger. Currently, 2 participants have completed both sessions and 3 participants have completed one session. Thus, the results reported here consider 3 participants in the "real" condition and 4 in the "sham" condition. Data analysis focused on changes in the I/O curve slopes from pre- to post-reaching task. Preliminary results show that the percent change of I/O curve slope is +51.2% (SE 32.5) for the "real" session, and -11.9% (SE 10.4) for the "sham" session. From this preliminary data, it appears that visuo-proprioceptive realignment may lead to a steeper I/O curve for a finger muscle that experiences sensory realignment. It is known that somatosensory and motor cortices have reciprocal anatomical connections. Taken together with what is described by Ostry et al. (2010), this novel result could indicate the existence of reciprocal functional interactions between motor and somatosensory systems.

Disclosures: F. Munoz: None. **A.K. Lynch:** None. **H.J. Block:** None.

Poster

795. Visually Guided Reaching and Eye Movements

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 795.07/O10

Topic: D.05. Visual Sensory-motor Processing

Title: Effects of gravitational signals on visuo-kinesthetic sensory transformations during hand movements

Authors: *M. TAGLIABUE[1,2], D. DAL CANTO[1,3], M. CASADIO[3], J. MCINTYRE[4,2,1];
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[4]IKERBASQUE Sci. Fndn., Bilbao, Spain

Abstract: Recent studies based on a virtual reality experimental paradigm suggest that head orientation affects not only the capacity of the brain to encode sensory information with respect to gravity, but also the effectiveness of transformations across sensory modalities that are needed to control goal oriented hand movements. For instance, when reaching for an object, the brain can be required to transform visual information about the object, intrinsically encoded in a retinal reference frame, to express it in a body-centered reference frame, so that it can be used to control the arm movement, whose position is inherently encoded in this reference frame. More precisely, we have shown that sensory transformations performed with the head tilted are noisier than those carried out with the head upright. Our hypothesis is that the gravity vector, which may be sensed through utricular signals, represents a stable reference frame through which the transformations between other sensory modalities are performed. It follows that the alignment of gravity and the references frames in which are encoded the available sensory signals (e.g. retina orientation, head/body axis) facilitates cross-modal transformations. To test whether the vestibular organs play a predominant role in the transformation of information between sensory modalities, we tested how a supine posture affects the execution of a task requiring visuo-kinesthetic transformations, such as reaching-to-grasp a visual target without visual feedback of the hand. To do so we applied the same virtual reality experimental protocol that we have used previously with seated subjects to subjects lying in a supine position and we compared performance between the two postures. The results show that movement variability is significantly greater in the supine than in the seated position. Moreover, the use of a special sensory conflict technique allowed us to estimate in which reference frame the sensory information is encoded. Subjects that performed the task in the sitting position first (Chair-First), showed a clear change of sensory encoding strategy when lying supine, which consisted of a shift from a kinesthetic body-centered toward an external visual encoding of the task. On the other hand, subjects that performed the task in the lying posture first (Bed-First) did not show consistent modifications of their sensory encoding strategy. This could be due to the fact than, whilst the Chair-First subjects had to face a ‘deprivation’ of a sensory input, which results in a necessity to change strategy, the Bed-First group faced the possibility, but not the necessity, to start using gravitational signals.

Disclosures: **M. Tagliabue:** None. **D. Dal Canto:** None. **M. Casadio:** None. **J. McIntyre:** None.

Poster

795. Visually Guided Reaching and Eye Movements

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 795.08/O11

Topic: D.05. Visual Sensory-motor Processing

Support: NS092079

Title: Compensating for a visuomotor rotation in the absence of sensory prediction errors

Authors: *D. E. PARVIN[1], R. J. MOREHEAD[2], R. IVRY[2];
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Abstract: Human motor adaptation is thought to occur via error based learning. Differences between predicted and actual sensory feedback are used to update an internal mapping to reduce errors on subsequent movements. One of the hallmarks of adaptation is an aftereffect, the persistence of the learned behavior after visual perturbation is removed. The magnitude of this aftereffect provides a measure of the extent of adaptation. Recent work has highlighted how multiple mechanisms, other than error-based learning, play a role in sensorimotor learning. It remains unclear how these mechanisms influence the aftereffect. In order to study non-adaptive contributions to the aftereffect, we trained participants on a variant of a visuomotor rotation task in which error-based learning was minimized. Participants were trained to reach to visual targets while receiving visual feedback of the hand via three cursors. One corresponded to the veridical position of the hand. The other two were displaced 15° clockwise and anti-clockwise of the hand position. During the perturbation phase the Adaptation group was instructed to hit the target with the middle cursor while all cursors were rotated by 15° in the clockwise direction. Here, the net rotation of all three cursors results in a 15° visuomotor discrepancy, which should engage an error-based learning mechanism. Participants in the non-adaptation group were instructed to hit the target with one of the side cursors. With this type of display, there is no visuomotor discrepancy and performance changes should occur in the absence of sensory prediction errors. Taken together, participants in the two groups should arrive at the same ideal behavior, allowing a comparison of the time course and form of behavioral change with and without error-based adaptation. We did not find a significant difference between the groups during learning of the rotation task. However, there was a significant aftereffect only for the Adaptation group. We conclude that the aftereffect was attributable to error based learning adapting to the net rotation of the three cursors. This three cursor paradigm can serve as a useful method to eliminate error-based learning from visuomotor rotation tasks, to better characterize non-adaptive learning mechanisms.

Disclosures: D.E. Parvin: None. **R.J. Morehead:** None. **R. Ivry:** None.

Poster

795. Visually Guided Reaching and Eye Movements

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Program#/Poster#: 795.09/O12

Topic: D.05. Visual Sensory-motor Processing

Support: NSF Grant 1358756

Johns Hopkins Science of Learning Institute

Title: Proceduralization of declarative knowledge in a motor adaptation task following prolonged training

Authors: *D. M. HUBERDEAU, J. W. KRAKAUER, A. M. HAITH;
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Abstract: When adapting to a perturbation of ones movements, human subjects typically exhibit savings, or faster re-adaptation when the same perturbation is seen more than once. This property of adaptation reflects a form of long-term memory, and understanding what underlies this change may help clarify how behaviors are learned in general. For instance, a recent study has shown that savings is attributable to a single component of learning (Haith, et. al., J. Neurosci, 2015). Specifically, adaptation exhibited during movements with sufficiently long reaction (RT) is more complete than when the RT is limited, and savings is only seen for trials with sufficient RT. Other recent studies have also shown a similar dissociation based on implicit and explicit learning processes (Huberdeau et al. *Curr Op Neurobiol*, 2015). Following only a single exposure to a perturbation, therefore, it seems that savings does not occur in the implicit component of adaptation. This raises the question, however, of whether savings could ever be obtained in this component. We first demonstrate that following repeated exposure to alternating perturbations, savings can in fact be realized when the RT is limited. What enables this change in the nature of savings under low-RT conditions? Is it due to a change in the learning rate of the implicit component, or does the explicit component consolidate such that it can be expressed at low-RT? We hypothesized that the expression of savings under limited RT following repeated exposures reflects the ability to more rapidly express an explicit strategy. To test this hypothesis, we sought to further differentiate between RT-sensitivity and the implicit process by also periodically instruct subjects to “reach directly for the target” within blocks of adaptation to a rotation (Benson, et. al. J Neurophysiol, 2011). Using this method, we found no evidence of savings in the implicit component, suggesting that savings in the low-RT condition reflects proceduralization of the explicit component (i.e. formation of a rapidly expressible stimulus-response association) rather than modulation of the learning rate of the implicit component. This

mechanism of proceduralizing declarative knowledge may be an important aspect of skill learning more generally.

Disclosures: **D.M. Huberdeau:** None. **J.W. Krakauer:** None. **A.M. Haith:** None.

Poster

795. Visually Guided Reaching and Eye Movements

Location: Hall A

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Program#/Poster#: 795.10/O13

Topic: D.05. Visual Sensory-motor Processing

Support: NSERC CREATE Grant 44931-2014

NSERC Discovery + Accelerator 249877-2006-RGPIN

Title: Hand and Tool positions differentially affect saccadic reaction times

Authors: *L. CARDINALI[1], T. R. MAKIN[3], J. C. CULHAM[2];
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[3]Hand and Brain Lab, fMRIB, Oxford Univ., Oxford, United Kingdom

Abstract: Eye-hand coordination is a fundamental part of efficient interaction with the environment. Previous studies showed a mutual influence of the eye and hand motor systems. Specifically, Thura et al. (2008) showed that saccadic reaction times (SRT) are modulated by whether the target appears close to or far from the participants' static hand position and whether participants perform the saccade immediately upon the target onset or following a 1-s delay. In our daily life, we perform many actions not just with the hand along but with a tool in hand. Here we wondered whether saccades would also be modulated by the position of a tool. We measured SRT to targets appearing in the right or left visual hemifield, close to or far from (1) a grabber tool (held with the right hand), (2) the participants' right hand, during a resting posture (palms down), or (3) the participants' right hand in an action posture (thumb-index finger pinch). In half of the trials participants were instructed to saccade toward the target at its appearance while in the other half we introduced a 1-s delay. We found that SRTs were modulated by the side in which the stimulus appeared, the presence of a delay, and the congruency between the target and the effector side. The tool condition and the pinch condition (where the motoric aspect of the posture was strengthened) showed similar patterns of SRTs compared to the static hand condition. These results suggest that the eye-effector link remains strong even during tool use

and they contribute to our understanding of how tool use is based on visuo-motor mechanisms for hand control.

Disclosures: **L. Cardinali:** None. **T.R. Makin:** None. **J.C. Culham:** None.

Poster

795. Visually Guided Reaching and Eye Movements

Location: Hall A

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Program#/Poster#: 795.11/O14

Topic: D.05. Visual Sensory-motor Processing

Title: Proprioceptive weights are independent of left and right hand sensory reliabilities

Authors: ***L. MIKULA**[1,2], L. PISELLA[2], G. BLOHM[3], A. Z. KHAN[1];
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Abstract: When planning to reach, information about both the target location as well as the initial hand position yield the movement vector. The initial hand position can be determined by proprioceptive information as well as visual information, if available. Bayesian integration posits that we utilize all information available, with greater weighting on the sense that is more reliable; thus generally weighting visual information more than the usually less reliable proprioceptive information. The neural mechanism by which information is weighted still remains unclear. It has been assumed that the weights are based on task- and effector-dependent sensory reliability requiring an explicit neuronal representation of variability. However, the weights could also be determined implicitly through learned modality-specific integration weights. While the former hypothesis predicts different proprioceptive weights for left and right hand, the latter predicts the same integration weights across the two arms. In order to discriminate between these two hypotheses, we designed two separate complementary tasks to measure the sensory variability for both vision and proprioception. Each task allowed us to assess the visual and proprioceptive variability either in a perceptual context (without reaching movements) or in a motor context. In addition, we applied prisms inducing a horizontal visual shift while participants were asked to point toward visual targets with both the left and right hands in separate trials. This third task was used to quantify the relative weighting given to each sensory modality when planning reaching movements. We found that the sensory weights for the left and right hands were extremely consistent regardless of large differences in sensory variability for the two hands, as measured in each of the two different contexts. Thus, we propose that weights for sensory

information during reaching are learned across both hands, rather than specific to each effector based on its variability.

Disclosures: **L. Mikula:** None. **L. Pisella:** None. **G. Blohm:** None. **A.Z. Khan:** None.

Poster

795. Visually Guided Reaching and Eye Movements

Location: Hall A

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Program#/Poster#: 795.12/O15

Topic: D.05. Visual Sensory-motor Processing

Support: R01HD059783

Title: Limb position drift indicates independent modules for planning movement vectors, and for representing limb configuration

Authors: ***J. R. PATTERSON**[1], R. SAINBURG[2,3], L. BROWN[4];
[2]Kinesiology, [1]Penn State Univ., State College, PA; [3]Neurol., Penn State Col. of Med., Hershey, PA; [4]Psychology, Trent Univ., Peterborough, ON, Canada

Abstract: We previously showed that when performing repetitive point-to point movements without visual feedback about hand position, the position of the arm drifts in space due to an accumulation of movement dependent errors (Brown et al, 2003). Regardless of participants' apparent lack of knowledge about their drift, joint torque patterns are progressively modified to maintain movement direction and extent over substantial changes in limb configuration. We now attempt to resolve this apparent paradox between knowledge of limb position for maintenance of posture and knowledge of limb configuration for control of movement. We hypothesize that planning of movement direction and distance depends on declarative knowledge of hand position, which depends on the last-seen position. In contrast, planning of movement dynamics depends upon updated and accurate proprioceptive information about actual hand position. In a VR environment, the arms were supported on an air sled apparatus to remove the effects of gravity and friction. Healthy young volunteers made continuous movements between two targets positioned 20 cm apart, paced by a 2 Hz metronome. After 20 cycles, cursor feedback of hand was removed for the next 160 cycles, which induced drift in the average hand position of roughly 6 cm. We then presented two new targets, and asked the participants to verbally identify which target is closest to their hand position, and then to move to that target. We hypothesized that if participants have declarative knowledge of their actual hand position, they will identify targets that are closest to their actual hand position, and if not, they will identify the target that is closest

to the original ‘start’ target. By assessing their movement, we will determine whether movements are planned and controlled based on the actual, or previously displayed hand position. Our preliminary results indicate that participants identify target positions that are closest to the previously displayed, not the actual, hand position and that movement direction and distance reflect planning from this same position. We conclude that participants do not have declarative knowledge about their drifted hand position, nor do they use the actual hand position in planning the direction and distance of their motion. Nevertheless, the ability to make accurate direction and distance movements suggest accurate proprioceptive information. Overall, these results support the premise that information about hand position is derived from different sources for different planning and control modules.

Disclosures: J.R. Patterson: None. **R. Sainburg:** None. **L. Brown:** None.

Poster

795. Visually Guided Reaching and Eye Movements

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Topic: D.05. Visual Sensory-motor Processing

Support: STW 12160

Title: Idiosyncratic matching errors cannot solely be explained by sensory biases

Authors: *I. A. KULING, M. C. W. VAN DER GRAAFF, E. BRENNER, J. B. J. SMEETS; VU Univ. Amsterdam, Amsterdam, Netherlands

Abstract: Moving one’s hand to a visually presented target on a surface under conditions that prevent one from seeing the hand generally results in idiosyncratic endpoint errors (e.g. Rincon-Gonzalez et al., 2011; Kuling et al., 2013). Do such matching errors reflect a mismatch between the senses due to stable sensory biases? If so, moving your unseen index finger to a visual dot or moving a visual dot to your unseen index finger should give rise to an equivalent matching error. Similarly, the error found when moving with the right and the left unseen index finger to a visual dot should be equivalent to the error when directly matching the position of the two unseen index fingers. To test these hypotheses, we designed a positioning task in which subjects had to indicate the location of a target on a surface with different indicators. The target was a visual dot or the left or right index finger and the indicator was the left or right index finger or a dot-shaped mouse cursor. We found that the matching errors for moving the unseen hand towards a visual dot differed considerably from those for moving a visual dot towards the hand. Also, the errors

found when moving with the right and the left unseen index finger to a visual dot do not lead to a similar error as matching the position of the two unseen index fingers directly. These results suggest that systematic matching errors are not exclusively the result of sensory biases.

Disclosures: I.A. Kuling: None. **M.C.W. van der Graaff:** None. **E. Brenner:** None. **J.B.J. Smeets:** None.

Poster

795. Visually Guided Reaching and Eye Movements

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Topic: D.05. Visual Sensory-motor Processing

Support: CIHR MOP-125915

Title: Cognitive-motor integration performance and cerebellum volume in females with post-concussion syndrome

Authors: *J. HURTUBISE, D. GORBET, L. SERGIO;
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Abstract: Cognitive-motor integration is often required when performing movements where a rule is used to align the required motor output and the guiding visual information. We propose that measuring this integration under conditions which place demands on visual-spatial and cognitive-motor processing may provide an effective behavioural means for detection of brain alterations associated with concussion. Our previous research has shown cognitive-motor integration declines in both university-aged and child athletes who had a history of concussion but were deemed recovered at the time of evaluation. The role of the cerebellum in sensorimotor integration has been well defined within the literature, however the effects of concussion on cerebellum functioning has not been thoroughly investigated. Cerebellar volume atrophy has been noted in both grey and white matter in moderate-to-severe traumatic brain injury patients, even when it was not the location of the focal injury. While recent murine models have suggested long-term cerebellar degradation following concussion (Kan et al. 2013), to our knowledge there has been no investigation of cerebellum volume in post-concussion syndrome (PCS) in humans. Here we examined cognitive-motor integration in females with PCS lasting more than 6 months at time of examination. Participants were administered the current international sport concussion assessment tool (SCAT3), along with four visuomotor transformation tasks (3 of which require cognitive-motor integration). In addition, anatomical

brain images were acquired using MRI. The behavioural tasks were completed on a tablet linked to a desktop computer monitor. The participants displaced a cursor from a central target to one of four peripheral targets by sliding their finger on the tablet either directly to the viewed target or with decoupled eye-hand coordination (targets viewed on vertical monitor, 180° cursor feedback rotation, or both). We observed that those with PCS had significantly worse symptom scores (both in number and severity) than controls, while no differences were found in any other aspect of the SCAT3. Those with PCS performed worse on the visuomotor tasks, with symptoms being correlated to this performance decline. Notably, cerebellar volume was decreased in those with PCS compared to controls. Cognitive-motor integration decline may be related to decreased cerebellum volume in these adults with PCS. Future work will investigate whether decreased connectivity involving the cerebellum is responsible for the volume differences seen in those with PCS. Ref: Kan, E. et al. (2013) SFN Abst#11.04.

Disclosures: J. Hurtubise: None. **D. Gorbet:** None. **L. Sergio:** None.

Poster

795. Visually Guided Reaching and Eye Movements

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Topic: D.05. Visual Sensory-motor Processing

Support: NSERC Grant

Trent University

Title: Comparing three tablet-based visuomotor tasks to standard laboratory versions

Authors: *C. BEDORE, J. LIVERMORE, H. LEHMANN, L. E. BROWN;
Trent Univ., Peterborough, ON, Canada

Abstract: The visuomotor system is important to everyday activity and assessment of its function can provide important information about neurological status. Although various visuomotor tasks are available for testing in the laboratory or clinic, attempts to make these tests portable so that quick and reliable psychometric assessments of performance can be conducted have been limited. We developed an assessment tool using three common laboratory visuomotor tests as a tablet (iPad) application: the double-step task, an interception task, and the stop-signal task. The double-step task measures participants' ability to redirect their reach to an unpredictable target displacement (Pelisson et al., 1986). The interception task measures

participants' ability to intercept accelerating targets (Brown et al., 2007). Finally, the stop-signal task measures participants' ability to interrupt movement preparation and initiation in response to an unpredictable stop signal (Logan, 1981). We compared performance of each task on the tablet to the standard laboratory setting. On the double-step task, participants adjusted to the displaced target adequately in both the lab and tablet versions. On the interception task, participants adequately intercepted non-accelerating targets, and performed worse on accelerating targets in both versions of the task. On the stop-signal task, participants' ability to interrupt movement initiation varied with the timing of the stop signal in a similar way in both versions of the task. These findings suggest that the tablet version of these tasks assesses similar visuomotor processing as the respective laboratory version. We now aim to assess the clinical usefulness and validity of the tablet tasks on patients with visuomotor deficits.

Disclosures: C. Bedore: None. **J. Livermore:** None. **H. Lehmann:** None. **L.E. Brown:** None.

Poster

795. Visually Guided Reaching and Eye Movements

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Topic: D.05. Visual Sensory-motor Processing

Support: IU School of Public Health Faculty Research Grant Program

Title: tDCS over somatosensory cortex alters the balance of visuo-proprioceptive weighting and realignment

Authors: Y. LIU[1], B. SEXTON[1], P. CELNIK[3], *H. J. BLOCK[1,2];
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Abstract: The human brain processes multisensory information to control voluntary movement. Visual and proprioceptive estimates of hand position are weighted and combined to compute a motor command to move the hand. Changes in vision or proprioception will thus affect multisensory processes, and ultimately motor behavior. E.g., if slicing an onion in a sink full of water, the brain's visual estimate of hand position is shifted away from proprioception by water refraction. A healthy person will compensate by adjusting the weighting of vision versus proprioception, by spatially realigning visual or proprioceptive estimates of hand position, or both. The minimum variance model suggests that realignment will be related to weighting: a person who relies heavily on vision will realign proprioception more and vision less, and vice

versa. This relationship is not obligatory, but exists in many cases, suggesting a role in multisensory precision and thus accurate motor control. Here we investigated visuo-proprioceptive weighting and realignment in healthy adults when proprioception related to the left hand was manipulated by applying excitatory or inhibitory transcranial direct current stimulation (tDCS) over right somatosensory cortex (S1), where proprioception for the left hand is processed centrally. Each subject completed 3 sessions with anodal (excitatory), cathodal (inhibitory), or sham tDCS over S1. Two blocks of reaches were completed with three target types: a white box (visual target), left index fingertip (proprioceptive target), or combined. During the adaptation block, a 70mm visuo-proprioceptive misalignment was imposed by gradually moving the visual target forward. No subject noticed this perturbation. Preliminary results (N=8) suggest that both anodal and cathodal tDCS increase the slope of the relationship between weighting and realignment relative to sham, meaning that for a given weight of vision versus proprioception, there is more visual and less proprioceptive realignment. Slope was 49.7, 99.5, and 94.0 for proprioceptive realignment versus weight; and -73.6, -93.6, and -109.9 for visual realignment versus weight (sham, cathodal, and anodal respectively; correlation R values for the tDCS sessions were > 0.8 or <-0.8; p-values < 0.01). This may be a function of changes in the proportion of visual versus proprioceptive realignment with different stimulation conditions. Interestingly, the slopes changed in the same direction for anodal and cathodal tDCS; it is possible that any external alteration of S1 physiology biases visuo-proprioceptive processing, or that tDCS has a non-specific effect.

Disclosures: **Y. Liu:** None. **B. Sexton:** None. **P. Celnik:** None. **H.J. Block:** None.

Poster

795. Visually Guided Reaching and Eye Movements

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 795.17/O20

Topic: D.05. Visual Sensory-motor Processing

Support: Ministero dell'Università e della Ricerca (MIUR) by Futuro in Ricerca (Protocollo: RBFR132BKP)

Fondazione del Monte di Bologna e Ravenna (Italy)

Title: Reaching target representation in the three-dimensional peripersonal space in the medial posterior parietal cortex

Authors: P. FATTORI[1], A. BOSCO[1], R. BREVEGLIERI[1], K. HADJIDIMITRAKIS[2], *C. GALLETTI[1];
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Abstract: The neural encoding of coordinate systems based on eye and target position in posterior parietal cortex has been traditionally studied in 2-dimensional plane, where the direction of movement was the only variable to consider in the computation of reaching metric. Only few studies focused on the combined influence of depth and direction on the definition of reference frame used by single neurons. Here we present single-unit data recorded from area V6A, a visuomotor area located in the caudal aspect of the superior parietal lobule, during a delayed and dissociated reaching task where eye and target positions varied both in direction and depth. We analysed the neural activity during pre-movement- and movement-related phases to establish whether cells encoded the target relative to the eye, encoded the target in spatiotopic coordinates, or on a mixed reference frame. We also analysed the interaction between depth and direction on the computation and the temporal evolution of reference frames. In all epochs studied, 12% of cells contained a pure reference frame centered on target position (spatiotopic or target-related coordinates), 24% was related on eye/target relative position (retinocentric or eye/target-related coordinates), and 63% to various types of mixed reference frame. Among the cells that used pure reference frames (target- and eye/target-related), some showed a competitive model where both representations were present but one prevailed on the other. In all categories, the modulation was found in depth, in direction or in both, covering the whole tested reaching space. The contribution of the two signals, depth and direction, to the definition of reference frame was characterized by a complex interaction in 85% of cells and by a gain relationship in 15% of cells. In the pre-movement epochs the resolution quality of reference frame was smaller compared with the movement-related phases, demonstrating a strong decrease of noise and variability during the movement execution with respect to planning phases. These data suggest that V6A contains different target representations that allow an accurate estimate of reaching positions in the 3D peripersonal space. This supports a dynamic and flexible encoding of reaching goals that allows the recruitment of neural patterns using different level of generalization depending on the sensory contingencies of external environment.

Disclosures: P. Fattori: None. **A. Bosco:** None. **R. Breveglieri:** None. **K. Hadjidimitrakis:** None. **C. Galletti:** None.

Poster

795. Visually Guided Reaching and Eye Movements

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Program#/Poster#: 795.18/O21

Topic: D.05. Visual Sensory-motor Processing

Support: NSERC 355931

Title: The effect of tool-vibration on unimanual reaching

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Abstract: Many workers are exposed to hand-arm vibrations while handling power tools. Previous research on exposure to hand grip mechanical vibrations have shown that frequencies up to 400 Hz affects sensory systems and can result in physiological and pathological disorders. The purpose of this study was to investigate how short-term exposure (< 10 minutes) to different frequencies of tool vibration influence arm reaching coordination. Four subject groups, each comprising ten right-handed healthy subjects, made 20 cm center-out planar arm reaching movements to two randomly-presented visual targets (target 1 oriented 60° relative to the horizontal axis and target 2 oriented at 120°). Each participant group experienced one of four vibration frequencies (40, 70, 100 or 115 Hz) while holding onto a custom-made pointing tool that was fitted with a vibration device. Each subject was given a practice session (10 trials) to familiarize with the task, followed by three blocks of 30 trials during which they experienced no-vibration (pre-exposure session), vibration (exposure session) and no-vibration (post-exposure session). Four measures were computed to examine group differences: movement distance error at final position, hand-path trajectory direction deviation, movement duration, and total distance traveled. We examined the effect of vibration on initial exposure and final adaptation assessing early and late trials on the vibration session. Preliminary data analysis showed that there was a main effect of target ($p < .001$) and epoch ($p = .013$) on movement distance, as well as an interaction between target and epoch ($p = .036$). Movement distance was shortened when vibration was first applied (mainly for 70 and 100 Hz frequencies), but subjects seemed to adapt and increase the distance traveled towards the end of the vibration experience. This effect was more evident for the 120° target and was confirmed by the increased variability on movement distance during baseline conditions and first exposure. Vibration influenced movement direction in a similar way, with main effects for target ($p < .001$), epoch ($p = .040$) and target-epoch interaction ($p = .002$). Following vibration, movements were faster and longer, and were accompanied by an increase in movement variability (distance and direction). These results suggest that tool vibration does influence arm reaching and should be studied further to fully determine its effects on upper limb coordination.

Disclosures: L.B. Bagesteiro: None. **L.E. Brown:** None.

Poster

795. Visually Guided Reaching and Eye Movements

Location: Hall A

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Program#/Poster#: 795.19/O22

Topic: D.05. Visual Sensory-motor Processing

Support: DFG Research Unit GA1475/4-1

Title: Movement planning in freely moving monkeys - the reach cage

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Abstract: Sensorimotor neuroscience investigates spatial parameters which influence neuronal sensorimotor processing, such as head position, gaze direction, and body posture. Especially in neuroscience with non-human primates, these requirements lead to highly specialized and controlled experimental setups with strongly constrained motor behavior. Typically, monkeys are seated in a primate chair and respond to sensory cues by operating a manipulandum or touchscreen, thereby limiting the type of behavior accessible to investigation to movements in the peripersonal space. Motor behavior to the extrapersonal space, i.e., beyond the immediate reach of the monkey requiring relocation towards the target, was prevented. Yet, studies on movement observation revealed mirror neurons [1] responsive for peripersonal or extrapersonal space in area F5 of rhesus monkeys, and human spatial neglect patients partly show deficits specific to either space [2,3], suggesting dedicated processing of extrapersonal space in brain areas related to motor control. Here, we introduce a neuroscientific experimental setting which allows comparing motor planning to targets in peripersonal and extrapersonal space. We developed a 1.4 cubic meter cage environment for conducting controlled sensorimotor tasks in physically unrestrained rhesus monkeys ("reach cage"). The reach cage is equipped with computer-controlled, capacitive touch sensors including multi-color LEDs serving as visually cued reach targets. As a first proof of concept, we trained the monkey on a memory-guided reach task to targets in peripersonal space inside the reach cage. We tracked the monkey's right hand movements with a video-based 3D-motion tracking system. As a result, hand trajectories could be tracked with 20 mm precision and 33 ms temporal resolution over the relevant workspace. Despite the animal not being physically constrained, movement trajectories and speed profiles were stereotyped and revealed typical properties of ballistic movements, similar to conventional chair-based task performance. Our results demonstrate that the reach cage is a valuable tool for

verifying conventional models of movement planning and control in a more complex environment and for expanding these models to movement planning in extrapersonal space. 1.Caggiano, V., et. al. Mirror neurons differentially encode the peripersonal and extrapersonal space of monkeys. Science 324, 403-406 (2009). 2.Halligan, P. W. & Marshall, J. C. Left neglect for near but not far space in man. Nature 350, 498-500 (1991). 3.Vuilleumier, P., et. al. Near and far visual space in unilateral neglect. Ann. Neurol. 43, 406-410 (1998).

Disclosures: **M. Berger:** None. **A. Gail:** None.

Poster

795. Visually Guided Reaching and Eye Movements

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Topic: D.05. Visual Sensory-motor Processing

Support: MSU College of Education Dissertation and Pilot-Study Research Support Fellowship

Title: Changes in motor cortical inhibition following a bimanual movement task

Authors: *A. T. BRUNFELDT[1], F. A. KAGERER[2,3];
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Abstract: Recent studies suggest hemispheric differences in the effectiveness of inhibitory processes in unimanual tasks. The goal of our study was to compare inhibition in both hemispheres before and after a bimanual movement task, using transcranial magnetic stimulation (TMS), and measuring short-interval intracortical inhibition (SICI). Six right-handed participants (mean age: 22.3) performed a bimanual center-out task, moving two KINARM end-point robots from two home positions (one per hand) to peripheral targets at 90º or 270º (distance: 10cm); vision of the hands was occluded. Participants performed a visual baseline condition, with both cursors visible, and a kinesthetic baseline (pre-exposure) where visual feedback was only present for the right hand, but not the left. They were then exposed to a 40o rotation of visual feedback in the right hand (exposure), and were instructed to continue moving straight with the 'invisible' left hand. Finally, the kinesthetic baseline condition was reintroduced to assess aftereffects of the adaptation. Initial directional error (IDE) was used to determine the feedforward directional control component of the movements. For TMS, resting and active (10% MVC) motor thresholds for the extensor digitorum were determined over each hemisphere, and recorded with surface electromyography (EMG). Cortical excitability and inhibition were determined prior to the adaptation task, using a single pulse paradigm set to elicit a 1mV peak-to-peak amplitude motor

evoked potential (MEP), and a paired-pulse paradigm for SICI at 2.5ms interstimulus interval. Inhibition was calculated as a percentage of the single pulse MEP (1mV) amplitude. MEP amplitude, obtained at the same stimulator output immediately after exposure was compared to pre-exposure. Preliminary results show a reduction of IDE over the exposure trials, indicating that the visible hand adapted to the kinematic perturbation, whereas the invisible hand showed small, yet consistent directional interference effects. No differences in cortical excitability before and after the adaptation task were found for either hemisphere. SICI, however, was modulated differentially for each hand, in that inhibition decreased (indicating disinhibition) more in the left hemisphere than in the right. This decreased disinhibition of the right motor cortex may reflect ongoing inhibitory mechanisms involved in control of the 'invisible' hand, in order to maintain a straight-line path, and resist the directional interference exerted by the concurrently moving perturbed contralateral hand.

Disclosures: A.T. Brunfeldt: None. **F.A. Kagerer:** None.

Poster

795. Visually Guided Reaching and Eye Movements

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Program#/Poster#: 795.21/O24

Topic: D.05. Visual Sensory-motor Processing

Support: NSERC Grant RGPIN-311680

CIHR grant MOP 93796

Title: Adaptation of ultra-rapid visual response on human upper limb muscle during visuomotor rotation

Authors: *C. GU[1,4,2], J. A. PRUSZYNSKI[3,4,5], P. L. GRIBBLE[3,4,2], B. D. CORNEIL[3,2,4,5]; [2]Psychology, [3]Physiol. and Pharmacol., [1]Univ. of Western Ontario, London, ON, Canada; [4]Brain and Mind Inst., London, ON, Canada; [5]Robarts Res. Inst., London, ON, Canada

Abstract: We have the ability to rapidly adapt our motor commands in novel environments. For example during the visuomotor rotation task, the sensory-mapping of the visual representation of the target is altered, so that a new motor command is required to accurately reach the target. Previous work has demonstrated an ultra-rapid (70-110 ms) stimulus-locked response (SLR) on human upper limb muscles to visual stimuli; furthermore this response also integrates proprioceptive limb position to generate the correct movement in limb-centric space towards the

visual target. Here we investigated the change in the tuning of the SLR pre- (no rotation), peri- (60° counter-clockwise [CCW] rotation) and post- (no rotation) visuomotor rotation in 8 subjects while they performed center-out reaches to 8 equidistance targets. While they performed the task we recorded intramuscular EMG activity from the clavicular head of the pectoralis muscle. 7 out of the 8 subjects had a SLR pre-visuomotor rotation, and the preferred direction (PD) of the SLR (176°± 4°) was similar to the PD of the movement-related activity (183° ± 6°) in the pre-condition. During the 60° CCW rotation, the movement-related activity rotated on average 56° ± 8° CW relative to the visual target to counteract the visuomotor rotation, however the SLR response rotated on average 17° ± 8° CW in the new adapted state. Post-visuomotor rotation, both the movement-related activity (0° ± 4° CCW compared to per-trials) and the SLR (3° ± 5° CCW) returned to the pre-visuomotor rotation PD. This result suggests that the neural circuits needed to perform the visuomotor rotation task influence the SLR.

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Poster

795. Visually Guided Reaching and Eye Movements

Location: Hall A

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Program#/Poster#: 795.22/O25

Topic: D.05. Visual Sensory-motor Processing

Support: DARPA Contract N66001-10-C-4056

Title: Varied tuning properties of single-units in human posterior parietal cortex during reach and saccade planning

Authors: *J. M. WEISS[1,2], W. M. MAGUIRE[1], A. P. BATISTA[2,3], J. L. COLLINGER[1,2,3,4], R. A. GAUNT[1,2];
[1]Physical Med. and Rehabil., [2]Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA; [3]Ctr. for the Neural Basis of Cognition, Pittsburgh, PA; [4]DVA, Pittsburgh, PA

Abstract: The posterior parietal cortex (PPC) is generally understood to be involved in multisensory integration and movement planning. In monkeys, the parietal reach region (PRR) is more active when planning reach than saccades [Snyder 1996], and encodes reach-plans in predominantly eye-centered coordinates [Batista 1999]. fMRI studies have suggested the existence of multiple analogous parietal reach regions in human PPC [Filimon et al., 2009]. Here we characterize the activity of individual neurons in human PPC. Under an FDA Investigational Device Exemption, a human subject with a C5 spinal cord injury was implanted with four Utah

Arrays (Blackrock Microsystems, Utah), including two 32-channel electrode arrays implanted in posterior parietal cortex. The subject performed (1) a delayed center-out reaching task, while maintaining fixation at either a central or peripheral point, (2) a delayed saccade task and (3) a coordinated saccade and anti-reach task. We characterized the tuning properties of units recorded during these tasks. By comparing the data from these three tasks we evaluated whether units were tuned for reaches or saccades, whether they exhibited target tuning that depended on gaze, and whether tuning favored the target location or the intended reach direction. We found that human PPC units have varied tuning characteristics, consistent with the notion that this cortical region is responsible for complex sensory integration. Units recorded from the more medial of the two arrays, located within Brodmann area 5, responded to the tasks in several ways. Most units responsive to reach direction also exhibited a weaker response to saccade direction. During both the delay and reach phases of the delayed-reaching tasks, some units had preferred directions that varied with gaze, while others maintained stable preferred directions regardless of changes in the direction of gaze. Preferred direction often varied throughout the delay period. This is especially true during the coordinated saccade and anti-reach task, in which many units exhibit a change in preferred direction approaching 180 degrees halfway through the delay period, from initially aligned with the target's visual location to aligned with the direction of the intended reach. Other units do not exhibit this shift in preferred direction, and are always tuned to the direction of the illuminated target. We also found units that encoded reach velocity, but did not respond to target presentations during the delay period. These varied results suggest that human posterior parietal cortex contains a diverse population of neurons encoding multiple aspects of visuomotor integration.

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Poster

795. Visually Guided Reaching and Eye Movements

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Topic: D.05. Visual Sensory-motor Processing

Support: National Doctoral Fellowship CONICYT, Chile

Biomedical Neuroscience Institute, Universidad de Chile

Title: Environmental constraints delay eye-hand coordination during a reaching task

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Abstract: Environment determines several aspects of the motor control. This is evident, for instance, during the realization of reaching movements, when visual feedback due in needed to guide hand displacements. Even though this sensorimotor coupling is well known, is still unclear how environmental characteristics may constraint sensory detection, planning and execution stages. Using a behavioral paradigm, we analyzed eye-hand coordination of twelve subjects during a classical reaching task to eight concentric locations. The contrast of targets relative to the background was managed to impose a visual constraint. Subjects must control a cursor on a screen while their eye movements were recorded with an eye-tracking system. Our results show that the reaction time of reaching movement, reflected by the cursor displacement, was greater at low-contrast in comparison with high-contrast targets (0.52 ± 0.09 s vs 0.46 ± 0.09 s, $p < 0.001$). As expected, saccades movements anticipated the reaching movements; however, the time difference between eye and hand movement was greater at the low-contrast than high-contrast targets (0.17 ± 0.1 s vs 0.13 ± 0.1 s, $p = 0.002$). This time-delay in planning did not impact the execution of movement, reflected in both reaching duration and angular displacement. Surprisingly, the time delay decreased with the practice of the task for both conditions, showing a narrow execution of eye and hand movement in the last stage. In case, the delay was significantly greater at the low-contrast target (0.09 ± 0.1 s vs 0.05 ± 0.09 s, $p = 0.03$), when we compare with the initial stage (0.23 ± 0.1 s vs 0.17 ± 0.1 s, $p = 0.19$). Overall, our experiments suggest that visual constraints delay the planning of reaching movements but not the sensory detection of its target or the execution of the reaching movement. These results indicate the necessity of more information to reduce the uncertainty of the target location. This necessity could be reduced with experience, reflecting an adaptation of the sensory processes to the environmental constraint in combination with the use of predictive mechanisms for movement planning.

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Poster

795. Visually Guided Reaching and Eye Movements

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Topic: D.05. Visual Sensory-motor Processing

Support: CNRS DEFISENS

CNRS PICS

Title: Movement kinematics and brain lateralization predict intermanual transfer of visuomotor, prismatic adaptation for each individual

Authors: ***F. R. SARLEGNA**, A. G. RENAULT, H. LEFUMAT, C. BOURDIN, L. BRINGOUX, J.-L. VERCHER;
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Abstract: Humans can adapt their motor behavior to various environmental conditions, yet it remains unclear which factors enable us to transfer what we have learned with one limb to the other. Previous work has shown the importance of factors such as the trained limb (Sainburg and Wang 2002; Criscimagna-Hemminger et al. 2003) or the nature of the perturbation (Malfait & Ostry 2004; Berniker & Kording 2008). Recently, we examined the intermanual transfer of Coriolis force adaptation: as in DiZio & Lackner (1995), subjects were asked to perform forward reaching movements with the upper limb toward flashed visual targets in pre-adaptation, adaptation and post-adaptation tests. Only the dominant arm was used during force-field adaptation and interlimb transfer was assessed by comparing performance of the non-dominant arm before and after exposure to the novel force field. On average, significant but limited transfer was observed, and we also uncovered a substantial heterogeneity of interlimb transfer across subjects. Critically, we showed that interlimb transfer can be qualitatively and quantitatively predicted for each healthy young individual based on his/her task performance, most notably motor variability and peak velocity during learning, and laterality quotient, a classic measure of brain lateralization (Oldfield 1971). Our study thus highlighted how individual characteristics shape the way the nervous system can generalize adaptation to a novel force field. However the differences between adaptation to a novel force field and adaptation to a visuo-motor transformation are well documented (Krakauer et al. 1999; Pipereit et al. 2006; Rabe et al. 2009). More recently, we thus hypothesized that intermanual transfer of prism adaptation (Harris 1963; Martin et al. 1996) is also determined by individual characteristics. We used the same paradigm as described previously except subjects had to adapt to prisms rather than to a novel force field. Preliminary results (N=20) indicate a large heterogeneity in interlimb transfer but still point toward the critical role of laterality quotient and peak velocity during the adaptation phase to predict generalization of sensorimotor adaptation across upper limbs.

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Poster

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Topic: D.05. Visual Sensory-motor Processing

Support: Stichting Technologie en Wetenschap (STW), Open Technology Program (OTP) grant 12668.

Title: Long-term motor adaptation: Time is not what matters

Authors: *K. VAN DER KOOIJ[1], K. E. OVERVLIET[2], J. B. J. SMEETS[3];
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Abstract: In this study we investigated how motor adaptation progresses over six sessions, performed over a two-week period. Motor adaptation is generally studied within sessions of about half an hour and its sub-processes have been found to occur on different time-scales. A fast process learns and forgets rapidly whereas another process learns slowly but has good retention (Smith et al., 2006). When repeating the experiment, some retention manifests itself as a changed initial baseline performance whereas other learning manifests itself as faster relearning, or savings (Krakauer & Shadmehr, 2006). However, it is not very well known how learning at different timescales compares to adaptation over the time course of days rather than minutes. We tested adaptation in a 3D pointing task in which subjects aligned their (unseen) hand with virtual red target cubes that were projected one by one at pseudo-random locations in 3D space. Terminal feedback was given by projecting a virtual feedback cube once a movement had ended. To introduce a bias that subjects had to adapt to, the tracked position of the hand was rotated by ten degrees around the cyclopean eye before rendering the feedback cube based on this position (equivalent to wearing wedge-prisms). A session consisted of five alternating blocks without and with feedback that allowed us to assess both learning from the feedback and forgetting of what had been learned. We analyzed the rate of learning and retention by fitting a two state - gain independent - multi rate model (Smith et al., 2006) to the data in the individual sessions. Our paradigm produced similar learning and retention as observed in earlier studies. Foremost, we found that forgetting (return to baseline) between sessions was much smaller than that predicted by a time-dependent retention rate, albeit somewhat larger than the forgetting that would be predicted by a trial-dependent retention rate. Second, we found that subjects improved their asymptotic level of adaptation by a small amount within each additional session of adaptation. We found no evidence of savings. Long-term adaptation could not be predicted by the retention

and learning rates of the first session, because retention appeared to be affect both by trial-dependent and time-dependent forgetting (which had a different time-constant).

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Poster

795. Visually Guided Reaching and Eye Movements

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Topic: D.05. Visual Sensory-motor Processing

Support: IRTG 1901 "The brain in action" (DFG)

Title: Reference frames for goal-directed reaching in natural scenes: The role of task relevance and scene coherence

Authors: ***M. KLINGHAMMER**[1], G. BLOHM[2], K. FIEHLER[1];
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Abstract: When interacting with objects in daily life situations, our brain relies on information represented in two main classes of reference frames: an egocentric (relative to the observer) and an allocentric (relative to objects or the environment) reference frame. In a recent study (Fiehler, Wolf, Klinghammer, & Blohm, 2014) we demonstrated that allocentric information is integrated into the movement plan when participants performed memory-guided reaching movements to targets surrounded by allocentric cues in a complex environment (i.e. images of a breakfast scene). In our current study, we aimed to investigate how task relevance and/or the coherence of the scene influence the integration of allocentric information into the movement plan. To this end, we presented participants 3D-rendered images of a breakfast scene on a computer screen with some objects on and some objects behind a table. Six of these objects served as possible reach targets and had to be learned before the experiment. Thus, the scene contained task-relevant and task-irrelevant objects. After free exploration of the encoding scene and a 1s delay, the test scene reappeared for 1.3s with one of the six possible targets missing. Moreover, task-relevant and task-irrelevant objects were shifted either to the left or to the right resulting in six different conditions: a) only relevant or b) only irrelevant objects were shifted in the same direction, c) relevant and irrelevant objects were shifted together in the same or d) opposite direction, e) only relevant or f) only irrelevant objects were shifted into opposite directions. After the test scene vanished, participants had to reach towards the memorized location of the missing

target on a grey screen. We predicted higher systematic deviations of reaching endpoints into the direction of the object shifts if task-relevant objects were shifted and the scene remained coherent (i.e. objects were shifted into the same direction) compared to conditions with shifts of task-irrelevant objects or with incoherent object shifts. We found stronger weighting of allocentric cues and higher precision of reaching endpoints in conditions with coherent shifts of only task-relevant objects but did not find an effect of coherence in conditions with shifts of only task-irrelevant objects. If task-relevant and task-irrelevant objects were shifted together, an object shift into the same direction led to higher weighting of allocentric cues compared to conditions with shifts in different directions. Our results demonstrate that task-relevance and image coherence are important, interacting factors for the integration of allocentric information for goal-directed reaching.

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Poster

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Support: NSERC

CIHR

NIH

Title: Bayesian integration of skewed distributions during sensorimotor learning

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Abstract: Both our sensorimotor system and the environment are full of uncertainty and nonlinearities. Our nervous system must account for these factors in order to produce accurate goal-directed movements. Research has shown that humans use: 1) Bayesian-like inference to minimize reach errors when perturbed by symmetrically uncertain, visual feedback, and 2) a sensorimotor loss-function that is robust to outliers. Unlike a symmetrical probability distribution (PD), a skewed PD can be used to find the underlying loss-function because it separates several

statistics. For example, the mean and median correspond to minimizing the squared or absolute error, while the mode maximizes the likelihood of a hitting a target. Currently, it is unknown if the nervous system can also integrate skewed uncertainty in a Bayesian way; and if so, what is the sensorimotor loss-function? To investigate, participants held a robot manipulandum as they performed reaching movements to a target. Participants had no vision of their arm. We informed participants that the visual feedback flashed halfway through a reach represented their hand position. Visual feedback was presented as either a single dot, a cloud of dots or withheld. For three different groups, visual feedback was laterally shifted according to a right-skewed, symmetric, or left-skewed PD. The mode of each PD was 0, 1 and 2 cm, respectively. The mean of each PD was shifted 1 cm rightward from the true hand position. As previously shown with symmetrical PDs, participants compensated for the 1 cm rightward shift by reaching 1.03 (+/- 0.07) cm leftward of the final target when visual feedback was withheld. Participants in the right- and left-skewed groups reached leftwards 0.92 (+/-0.07) and 1.12 (+/- 0.05) cm when no feedback was given. Both of these values are between the mean and median, and are inline with a loss-function robust to outliers. Interestingly, however, this strategy caused participants in the skewed PD groups to miss the final target when visual feedback was withheld. Our data show that the nervous system can integrate skewed uncertainty in a Bayesian-like way, and uses a loss-function robust to outliers at the expense of maximizing the likelihood of success.

Disclosures: **J.G. Cashaback:** None. **A. Mohatarem:** None. **H.R. McGregor:** None. **P.L. Gribble:** None.

Poster

795. Visually Guided Reaching and Eye Movements

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Topic: D.05. Visual Sensory-motor Processing

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R01-EY024067

NSF BCS 0955701

Title: A coordinated saccade with a reach increases reach accuracy in the absence of target foveation

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Abstract: In primates looking and reaching to the same target is a common behavior leading to precise reaching. Several factors contribute to precise reaching. When targets are constantly visible, the saccade foveates the target before the hand arrives. Furthermore, evidence from neural recordings suggests that when coordinated eye and reach movements (i.e. saccade and reach to the same spatial location) occur, both the saccade and reach systems interact. If so, coordinated saccadic eye movement planning may influence the plan and execution of the reach movement and improve reach accuracy. Importantly, this improvement due to a coordinated saccade should occur in the absence of target foveation. In order to assess the contribution of a coordinated saccade to reach accuracy we tested reach accuracy under four different conditions: 1) when a reach is coordinated with a saccade to a visual target (delayed-reach-and-saccade: DRS); 2) when a reach to a visual target is performed while keeping central fixation (delayed-reach-and-fixation: DRF); 3) when a reach is coordinated with a saccade to a remembered target (memory-reach-and-saccade: MRS); and 4) when a reach to a remembered target is performed while keeping central fixation (memory-reach-and-fixation: MRF). We found that reach accuracy is improved by adding a saccade without any visual information about the target (MRS trials). Accuracy is improved to a level similar as having peripheral vision of the target without the saccade (MRF trials).The hand mean error for MRS (*1.76° ± 0.03°)* trials was significant smaller in comparison to the DRF (*2.31° ± 0.04°*) and MRF (*2.95° ± 0.04°)*, but significantly larger than the DRS (*1.5° ± 0.02°;* one-way ANOVA, p=2e-176, F=302.44, df=3, Bonferroni corrected, n=967 trials). This finding could be explained by: 1) interaction between the saccade and the reach system, leading to a common motor plan, 2) interaction between the reach system and the saccade efferent copy, proprioceptive signals or a combination of both, 3) hand foveation leading to online reach corrections, and 4) a mixture of the above.

Disclosures: Y. Vázquez Zúniga: None. **D.J. Hawellek:** None. **B. Pesaran:** None.

Poster

795. Visually Guided Reaching and Eye Movements

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Topic: D.05. Visual Sensory-motor Processing

Support: CSIR

NBRC

DBT

IISc

Title: Eye-hand coordination in visual search

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Abstract: In the context of coordinated eye-hand movements, previous work from the lab, using a combination of eye and hand reaction time (RT) measures, electromyography (EMG) and drift diffusion model in pointing and redirect task has suggested that brain employs a common network for coordinated eye-hand movements (Gopal et al., 2015). One of the striking observations was that mean hand RT was greater than eye RT but their standard deviations (SD) were similar. This cannot be explained by considering two separate drift diffusion processes for eye and hand each with different drift rates, as the drift diffusion model suggests that the SD of the accumulation process scales along with the mean. Further, the correlation between eye and hand RT was high. These suggested that both eye and hand movements were generated by a common motor command (CC model) with the delay in hand muscle activation (motor delay) resulting in increased mean hand RT compared to mean eye RT. Here we investigated the ability of CC model to explain coordinated eye-hand movements, when the task involved a more complicated decision i.e. a visual search task where the target would be hidden among distractors. 10 naive subjects were instructed to make eye-hand movement to the target located among 3 distractors. There were alternating simple and difficult search blocks, each having 12-20 trials, with the simple block having red and green colours and the difficult block having green and blue-green colours. Further the colour of the target and distractor was randomly swapped. Correct trials were trials in which the direction of the first saccade and the direction of first hand movement, was in the direction of the target, while error trials were those in which either of the two movements was towards a distractor. Subjects fared better in simple search than difficult search with mean eye and hand RT and error % increasing in the difficult trials. Further mean hand RT was greater than mean eye RT in both conditions; however their SDs were similar ($p>0.05$ for both conditions), as predicted by the CC model. The Pearson's correlation between eye and hand RT was moderate to high for all subjects as predicted by the CC model (Easy: mean = 0.51; Difficult: mean = 0.71). We also found that the %dissociated trials (the direction of the first saccade and first hand movement was different) was strongly correlated with the difference in SD of eye and hand RT ($r = 0.59$, $p = 0.006$), suggesting that when the CC model was not applicable the chance of independent eye and hand movements increased. These results suggest that the CC model can be extended from coordinated eye-hand movements during pointing to movements which involve a more complicated decision.

Disclosures: **S. Jana:** None. **A. Gopal:** None. **A. Murthy:** None.

Poster

795. Visually Guided Reaching and Eye Movements

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Topic: D.05. Visual Sensory-motor Processing

Title: Mirror-reversed visual feedback reduces quick somatomotor response evoked by mechanical perturbation

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Abstract: Quick somatomotor response evoked by mechanical perturbation (stretch reflexes) is flexibly modulated depending on environmental dynamics. For instance, long-latency stretch response is adjusted to a novel dynamics after an adaptation to a force field (Cluff & Scott 2013). It is, however, still unknown whether or not somatomotor response is modulated by an exposure of a novel visuomotor environment. Previous research showed that somatosensory evoked potentials are cortically suppressed by giving a mirror-reversed vision (Bernier et al. 2009). From this observation, it could be inferred that somatomotor responses decrease by giving a novel visuomotor relationship, in addition to the reduction of visuomotor response (Gritsenko & Kalaska 2010). To examine this prediction, we asked participants to make a one-dimensional reaching movement (45 deg, wrist flexion) with normal (NVF) or mirrored (MVF) visual feedback of fingertip position. To examine the quick visuomotor and somatomotor responses, we applied target jumps (positive and negative) and mechanical perturbation, respectively, during the movements (random trial order). Participants were required to correct their reaching movement toward the new target location as quickly as possible (Pro-task). The visuomotor response was evaluated by the acceleration deviation to the new target, and somatomotor response was evaluated by the muscle activities of wrist flexor and extensor. In addition, we also acquired these responses in the anti-correction task for target jumps (Anti-task) with NVF, by which the quick visuomotor response would decrease (Day & Lyon 2000). As a result, we observed longer latencies of visuomotor responses both for Pro-task with MVF and for Anti-task with NVF, as in the previous studies. In contrast, we found a significant reduction of the long-latency somatomotor response (50-100[ms] after perturbation) during the Pro-task with MVF, while no significant reduction was found during Anti-task with NVF. These results suggest that visuomotor and somatomotor responses are not always synchronously modulated. Considering the comparable delay in visuomotor responses in Anti-task with NVF and in Pro-task with MVF, the decrease in somatomotor responses in the MVF condition was not accounted for by an

increased task difficulty (cognitive load). We conclude that the observed decrease in somatomotor response is attributed to the strong visuomotor discordance due to the mirrored visual feedback.

Disclosures: S. Ito: None. **H. Gomi:** None.

Poster

796. Itch

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Topic: D.08. Pain

Support: MOST103-2325-B-001-015

MOST103-2321-B-001-037

Title: Acid induced itch and the roles of proton-sensing ion channels in pruritoception

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Abstract: Itch and pain are closely related but distinct sensations. Intradermal injection of acid generates pain in both rodents and human; however, few studies address the intriguing issue whether protons can be regarded as a pruritogen as well. We reported here that acid (in 0.2M citric acid) pH-dependently induced scratching response in mice when applied intradermally to the neck skin. In the cheek assay, citric acid (pH=3.0) induced both scratching and wiping/digging behavior when compared with the well-known pruritogen “chloroquine” and algogen “capsaicin”, respectively. Like the action of many other pruritogens, acid at pH3.0 elevated intracellular calcium in a small population of TRPV1-positive DRG neurons. These results implicated that proton could be a potent pruritogen apart from its well known role as an algogen. To identify the target acid-sensing receptor that is involved in the proton-evoked itch, we screened phenotypes in the citric acid-induced itch model with several mutant mice lines lacking a proton-sensing ion channel, such as ASIC1a, ASIC2, ASIC3, ASIC4, TRPV1, or TRPA1. Results indicated that acid-induced itch could be separated into two phases: (1) the first acute phase (~5 minutes) was mediated by TRPV1 in a pH-independent manner; (2) the later prolonged phase (5-30 minutes) was TRPV1-independent and the scratching response was

increased in a pH-dependent manner. Compared with WT mice, acid-induced scratching response was specifically decreased in the first acute phase in TrpV1-/-. Normal acid-induced itch response was observed in TrpA1-/-, Asic3-/- and Asic4-/- mice. Our results provide the first evidence that proton is a potent pruritogen and intradermal administration of proton can evoke itch response. TRPV1, but neither TRPA1 nor ASICs, initially mediates the scratching response induced by acid.

Disclosures: **S. Lin:** None. **C. Chen:** None.

Poster

796. Itch

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Support: Duke Anesthesiology 2015 DIG Grant 2015-DIG LIU

NIH Grant R01 ES015056

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Title: Exploring the mechanisms of itch and skin inflammation of poison ivy contact dermatitis

Authors: ***B. LIU**, Y. TAI, S. ACHANTA, A. CACERES, M. KAELBERER, P. BONNER, S. JORDT;
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Abstract: Background: Allergic contact dermatitis (ACD) is a common skin condition triggered by environmental or occupational allergens. In the US, the most common ACD is caused by contact with poison ivy, with more than 10 million cases each year. The major clinical manifestations of poison ivy-induced ACD are characterized by skin rashes, swelling, severe itch (pruritus). However, still little is known about the detailed immune and pruritus mechanisms involved in poison ivy-induced ACD. Objective: We aim to explore the mechanisms underlying poison ivy-induced skin inflammation and severe pruritus. Methods: We established a mouse model of poison ivy-induced ACD using the major allergen in poison ivy−urushiol. We compared the macroscopic features of dermatitis induced by urushiol with the widely used experimental allergen oxazolone by means of pathology scoring and transepidermal water loss (TEWL). The cellular immune responses and endogenous pruritogens were examined by transcriptome microarray, qPCR, ELISA and immunohistochemistry. Behavioral assays were

also performed to judge the pruritus responses of the mice. Results: The mice treated with urushiol developed skin inflammation and intense scratching behaviors. Compared with oxazolone, urushiol induced stronger skin swelling, erythema and TEWL changes. In terms of cellular immune responses, oxazolone showed potent inductions of Th1/Th2 components, while urushiol demonstrated a strong TH2 bias and some TH17 contributions. We also identified specific endogenous pruritogens as possible mediators of pruritus responses in the urushiol model. Conclusion: This mouse model we established recapitulates many key features of human poison ivy ACD. We believe our study will unravel the mechanisms of skin inflammation and pruritus in poison ivy-induced ACD and provide a wider range of therapeutic options.

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Poster

796. Itch

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Title: The role of itch receptors in reflex bronchoconstriction

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Abstract: The respiratory system is densely innervated by vagal sensory neurons. However, to what extent the vagal sensory neurons contribute to the development of respiratory diseases is largely unknown. Mrgprs (Mas-related G protein-coupled receptors) are a family of GPCRs consisting of more than 50 members in the mouse genome. Based on sequence homology, Mrgprs can be grouped into several subfamilies: MrgprAs, MrgprBs, MrgprCs, and MrgprD-G. Our previous studies have demonstrated that Mrgprs are expressed in subsets of DRG sensory neurons mediating itch sensation in the skin. Recently we found that itch receptors Mrgprs are

also expressed in subpopulations of vagal sensory neurons. Neuronal retrograde tracing showed that MrgprC11+ vagal sensory neurons innervate the airway. Application of MrgprC11 agonist, Bam 8-22 peptide, induced a significant increase in airway resistance (Rrs) which could be blocked by vagotomy and cholinergic blocker (ipratropium bromide). These results demonstrated that activation of MrgprC11+ vagal sensory nerves in the airway evoked cholinergic reflex bronchoconstriction. Moreover, HDM-induced allergic inflammation in the airway enhanced the expression of itch receptors in vagal sensory neurons. Interestingly, pretreatment of the animal with Bam8-22 significantly increased the airway sensitivity to MCh. Our results thus indicate the role of itch receptor Mrgprs in the pathogenesis of airway hyperresponsiveness.

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Poster

796. Itch

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Title: The voltage-gated potassium channels contribute to regulation of physiological function in mrgpra3 specific itch neurons

Authors: *Z. TANG[1], M. TANG[3], G. WU[2], Y. GUAN[4], X. DONG[5], Z. WANG[2], N. YANG[2], H. SHI[2], Q. HE[2], G. YU[2], C. ZHU[2], Y. YANG[2], C. WANG[2], X. YUAN[2];
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Abstract: Itch is described as an unpleasant or irritating skin sensation that elicits the desire or reflex to scratch. MrgprA3, a member in Mrgprs family, specifically expresses in a subpopulation of dorsal root ganglion (DRG) in peripheral nervous system (PNS). These DRG neurons, which express MrgprA3, were identified as itch-specific neurons. They could be induced by a compound named as chloroquine which was used as a drug to treat malaria. In the present study, we labeled these itch-specific neurons through using the method of molecular

genetic marker, and studied their electrophysiological properties. We firstly found that MrgprA3 could negatively regulate the excitability of DRG neurons. The number of action potential (AP) was obviously reduced in MrgprA3 positive (MrgprA3+) neurons than in MrgprA3 negative (MrgprA3-) neurons when a train of depolarizing steps current (Δ=20 pA) with 200ms duration were applied to induce AP generation. In most cases, MrgprA3+ neurons only generated single AP, however, in MrgprA3- neurons, the same stimulation could induce multiple AP firing. The reason was the greater voltage-gated potassium (Kv) current existed in MrgpA3+ than in MrgprA3- neurons. Thus, the Kv current plays an important role in regulation of excitability itch-specific neurons.

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Poster

796. Itch

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Title: Neurotrophic factors selectively modulate scratching behavior and sensory neuron responses to pruritogens

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Abstract: Neurotrophic factors such as nerve growth factor (NGF) and the glial cell line-derived neurotrophic factor (GDNF) family of ligands can modulate nociceptor structure and function, but little is known about how they may affect itch. Skin samples from patients with chronic itch conditions such as atopic dermatitis or psoriasis exhibit increased intraepidermal nerve fiber density, increased GDNF and artemin, and increased NGF and its receptor TrkA. Additionally,

we have recently demonstrated a selective increase in fibers expressing Ret, the receptor for GDNF family ligands (GFLs), in a mouse model of dry skin itch. Based on these findings we hypothesized that neurotrophic factors (NTFs) contribute to the development and maintenance of chronic itch. In our current studies we investigated whether NGF and the GFLs GDNF, neurturin, and artemin can directly induce or modulate histaminergic and non-histaminergic itch. First, scratching and wiping behavior after intradermal injection of NTFs into the cheek skin of mice was quantified to determine whether NTFs alone can induce pain or itch. The effects of acute and chronic NTF pretreatment on histamine- and chloroquine-induced scratching were also determined. We found that acutely injected NTFs did not induce scratching or wiping behavior by themselves. Chronic NTF treatment also did not alter spontaneous scratching or wiping behavior. On the other hand, acute 1 hour pretreatment with NGF selectively potentiated histamine-induced scratching, while artemin potentiated chloroquine-induced scratching. To elucidate the mechanisms by which specific NTFs potentiate histaminergic and histamine-independent itch, dissociated trigeminal ganglion neurons from Ret-eGFP reporter mice were pre-incubated with NTFs and examined for calcium responses to pruritogens and transient receptor potential (TRP) channel agonists. Our ongoing studies suggest that NTFs modulate the peak calcium responses and overall proportion of sensory neurons that respond to pruritogens.

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Poster

796. Itch

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NS089130

Title: Human sensory neuron: a novel strategy for translational approaches to pain and itch

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[2]Anesthesiol., Univ. of Cincinnati Med. Ctr., Cincinnati, OH

Abstract: Biological differences in sensory processing between human and model organisms may present significant obstacles to translational approaches in treating chronic pain and itch. Such obstacles may include functional differences in target receptor pharmacology and signaling or fundamental differences in neuronal physiology. Although cultures of rodent dorsal root ganglion (rDRG) neurons have proven useful for identifying new analgesic targets and elucidating signaling pathways, notable translational failures have recently raised questions about the wisdom of developing drugs for pain relief in rodents for eventual use in humans. While limited evidence suggests that questions regarding human sensory neuron physiology may be addressed in recordings from cultured human DRG, tissue is often obtained from patients with chronic pain or before the nervous system has fully developed. We recently reported the first study of the electrophysiological properties of cultured human sensory neurons from young-adult donors without chronic pain, indicating that these types of studies are feasible and could be a powerful approach to understanding the biology of human neurons and development of novel therapeutic strategies. We have now developed an approach to culture human sensory neurons in our lab and perform a variety of molecular biology, imaging, and electrophysiological experiments to develop a comprehensive picture of their neurobiology. We have begun to use single-cell RT-PCR to assess the transcriptional profile of ion channels, receptors, and other signaling molecules in individual neurons to correlate their expression with the electrophysiological properties and channel conductances from individual neurons. Using both whole-cell recordings and calcium imaging, we are now characterizing excitability signatures and population responses to algogens, pruritogens, and other neuro-active molecules to understand the chemosensitivity of these sensory neurons, with the long-term goal of correlating these signatures to patients' medical history of chronic pain or itch. We have also been successful in co-culturing human DRG with non-neuronal human keratinocytes, to investigate whether signaling cross-talk and sensitization may occur, especially in cases of chronic itch. We anticipate that these approaches will be very informative of the underlying neurobiology of human DRG and allow for the improved translational outcomes.

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Poster

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Title: Activation of trpv4-expressing resident cells in the skin promotes itch

Authors: *J. LUO[1], G. YU[1], J. DU[2], W. YU[3], A. QIAN[4], J. FENG[1], Y. ZHANG[5], P. YANG[1], M. MACK[1], S. LIU[1], S. YIN[7], J. CHENG[8], R. G. O'NEIL[6], Q. LIU[9], Y. XIA[5], B. S. KIM[1], S. M. CARLTON[2], Q. LIU[1], H. HU[1];
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Abstract: Chronic itch is a major clinical issue involving both allergic and non-allergic mechanisms. Although cutaneous cells play critical roles in skin barrier function and immune surveillance, their role in the pathogenesis of chronic itch is not fully understood. Here we show that activation of transient receptor potential vanilloid 4 (TRPV4) channels expressed by skin keratinocytes and innate immune cells is sufficient to generate a scratching response. More importantly, spontaneous scratching in mouse models of both chronic dry skin itch and allergic contact dermatitis, which recapitulates symptoms of skin disorders in humans, is also severely reduced by genetic ablation of the TRPV4 function. Most importantly, platelet- but not mast cell-derived serotonin is required for generating TRPV4-mediated scratching. Our study reveals a unique function of the TRPV4-expressing cutaneous cells in the genesis of both acute and chronic itch and might provide new insights into the development of effective therapies for chronic itch.

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Poster

796. Itch

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Topic: B.02. Ligand-Gated Ion Channels

Title: Activation of T-type Ca^{2+} channel regulates PAR2 dependent allergic contact dermatitis

Authors: *Y. KIM, S. CHUNG;
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Abstract: Activation of T-type Ca^{2+} channel regulates PAR2 dependent allergic contact dermatitis The protease-activated receptor (PAR)2, a family of G-protein coupled receptors, is expressed on peripheral sensory neurons and its activation evokes itching, but its cellular mechanism is still unknown. Recently, it has been reported that T-type Ca^{2+} channel contribute to nociception and augmentation of T-type calcium current (I_{ca-T}) may evoke itching by sensitizing peripheral nociceptors. So we hypothesized that a PAR2-induced itching may be due to sensitization of primary sensory DRG neurons evoked by augmentation of I_{ca-T}. Either trypsin (300 nM) or PAR2-activaing peptide H-Ser-Leu-Ile-Gly-Arg-Leu-NH2 (SL-NH2) (100 μM), augmented Ica-T in phospholipase C (PLC)- dependent but, Ca^{2+} and protein kinase C (PKC)-independent manners. In current-clamp experiments, PAR2 agonists increased after depolarizing potential (ADPs) and this effect was completely inhibited by application of mibefradil, a potent T-type channel blocker. In addition, trypsin increased excitability by lowering the threshold for AP firing even at the physiological resting membrane potential (RMP). Mibefradil reversed the effects of trypsin (300 nM). Finally, intraplantar (i.pl.) injection of PAR2 agonists lowered paw withdrawal threshold (PWT) compared to that of vehicle-treated rats. This reduced PWT was completely reversed by co-treatment of mebefradil. These observations suggest that PAR2 activation readily augment I_{ca-T} in peripheral nociceptive neurons and this augmentation of I_{ca-T} may be involved at least, in part, in PAR2-evoked itching.

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Poster

796. Itch

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 796.09/O42

Topic: D.08. Pain

Support: CIHR

NSERC

QPRN

LAEF

Title: A chemogenetic model for studying itch in awake mice

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Abstract: Itch, or pruritus, can be described as an unpleasant sensation that leads to scratching behavior or the desire to scratch. Due to high prevalence in numerous diseases and widespread occurrence as a side effect of many medications, itch has become a research topic of choice in recent years. Despite significant structural and behavioral overlap of pruriception and nociception, the underlying neurophysiological basis of itch sensation and its relation to pain remain unclear. Taking advantage of chemogenetic tools with Cre recombination-based transgene expression and viral gene delivery methods, we targeted the Gq-coupled DREADD, HM3D, selectively to the MrgprA3-expressing peripheral afferent subpopulation. HM3D is an engineered muscarinic receptor activated solely by the inert ligand clozapine N-oxide (CNO). The target primary nociceptors, expressing the chloroquine receptor MrgprA3, constitute a subpopulation of afferents specifically linked to itch (Han et al., 2013). Selective expression and trafficking of HM3D-mCherry to the surface and terminals of MrgprA3 neurons were validated in fluorescence microscopy. Functionality of HM3D was also validated using electrophysiology and calcium imaging on dissociated DRG neurons *in vitro*. Injection of CNO in the skin of transgenic mice expressing HM3D in MrgprA3 neurons induces robust itch responses. Using the cheek model of itch (Shimada and LaMotte, 2008), we observed that CNO injection evokes stereotypical itch behavior (scratching with the hind paw) rather than pain response (wiping with the forepaw). These results confirm the unique properties of this small population of C-fibers and validate a novel model to investigate the cellular and molecular basis for itch sensation. Combined with optogenetic techniques to gain high spatiotemporal precision, the chemogenetic control of MrgprA3 neurons provides a powerful *in vivo* tool for studying the mechanisms of discrimination between itch and pain in the somatosensory system.

Disclosures: B. Sharif: None. **X. Dong:** None. **P.A. Seguela:** None.

Poster

796. Itch

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: D.08. Pain

Support: CIHR

NSERC

QPRN

FRSQ

Title: Chemogenetic sensitization of pain pathways in freely moving animals

Authors: *H. ALKHANI, P. SEGUELA;
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Abstract: Pain is an unpleasant acute or chronic sensation experienced following peripheral injury, inflammation or ischemia. Current models used to investigate pain behaviors in rodents are plagued with pitfalls ranging from lack of spatiotemporal specificity to mandatory invasiveness. Here, we report a novel transgenic mouse model based on hM3D (Gq-coupled DREADD)-mediated sensitization of peripheral nociceptive pathways in virally-transduced Nav1.8(+) nociceptors, without administration of any external noxious stimuli or injury. Systemic activation of hM3D induced by intraperitoneal clozapine N-oxide (CNO) injections evoked strong nocifensive behavior with reduced locomotion, squinting of the eyes and ruffled fur. Intradermal paw injections of CNO resulted in robust acute thermal and mechanical sensitization as measured in Hargreaves and Von Frey tests. Moreover, CNO induced edema and redness in the injected paws, indicating the activation of neurogenic inflammatory mechanisms similarly observed in sensitization protocols with capsaicin. The observed nocifensive behaviors appear to be specifically due to the contribution of small and medium diameter Nav1.8(+) DRG neurons, as indicated by our histology data, with fiber projections limited to the lamina I and II layers of the dorsal horn of spinal cord. These findings demonstrate for the first time the chemogenetic control of peripheral sensitization in behaving mammals and enables selective activation of the same class of afferents *in vivo*. Our results provide a proof-of-concept demonstration that chemogenetic interrogation of the contribution of specific classes of genetically-identified primary afferents to peripheral sensitization is possible. Non-invasive chemogenetic rodent pain models combining effective spatial penetrance with neuronal specificity have the potential to facilitate drug development and target validation for migraine or chronic pain relief.

Disclosures: H. Alkhani: None. **P. Seguela:** None.

Poster

796. Itch

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Support: NIH Grant RO1RGM101218A

China Scholarship funding

Title: Eact, a small molecule activator of ANO1, activates TRPV1 and elicits pain- and itch-related behaviors

Authors: J. FENG[1], S. LIU[1], J. LUO[1], P. YANG[1], *H. HU[2];
[1]Anesthesiol., [2]Washington Univ. in St. Louis, St. Louis, MO

Abstract: TMEM16A, also known as anoctamin 1 (ANO1) channel, is a member of the Ca2+-activated chloride channels (CaCCs) family, and serves as a heat sensor in the primary nociceptors by detecting noxious thermal stimuli. Eact is a recently discovered small molecule activator of ANO1. We thus asked if Eact produces sensory hypersensitivity *in vivo* and investigated the cellular and molecular basis of Eact-mediated responses in primary sensory neurons. We performed behavioral testing combined with pharmacological inhibition and genetic ablation studies to identify molecules responsible for Eact-evoked itch- or pain-related responses. We performed Ca2+ imaging and patch-clamp recordings to investigate the effects of Eact on ion channels heterologously expressed in HEK293T cells and endogenously expressed in dorsal root ganglia (DRG) neurons isolated from wild-type (wt) and TRPV1 (transient receptor potential vanilloid 1)-deficient mice. We also used site-directed mutagenesis of TRPV1 channel to determine the structural basis of Eact-mediated responses. Administration of Eact elicited both itch- and pain-related behaviors. Unexpectedly, the Eact-elicited sensory hypersensitivity was dependent on the function of TRPV1 as shown by pharmacological inhibition and genetic ablation studies. Eact activated membrane currents and evoked intracellular free Ca2+ increase in both TRPV1-expressing HEK293T cells and isolated DRG neurons in a TRPV1-dependent manner. Mutations disrupting the capsaicin-binding sites severely attenuated Eact activation of the TRPV1 channel. Our results suggest that Eact activates primary sensory nociceptors and produces pain and itch sensations mainly through direct activation of TRPV1.

Disclosures: **J. Feng:** None. **S. Liu:** None. **J. Luo:** None. **P. Yang:** None. **H. Hu:** None.

Poster

796. Itch

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Topic: B.04. Ion Channels

Support: NRF Grant 20110018358

BK21+ Program of Ministry of Education of Korea

Title: Identification of ion channels involved in compound 48/80 mediated degranulation of mast cells

Authors: *B. LEE[1], H. CHUN[2], H. KIM[2], J. WEE[2], I. CHOI[2], U. OH[2,3];
[1]Seoul Natl. Univ., Seoul, Korea, Republic of; [2]Sensory Res. Center, Creative Res. Initiatives, Col. of Pharmacy, Seoul Natl. Univ., Seoul, Korea, Republic of; [3]Dept. of Mol. Med. and Biopharmaceutical Sciences, Grad. Sch. of Convergence Sci. and Technology, Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Compound 48/80 is a mixed polymer of p-methoxy-N-methyl phenylethylamine crosslinked by formaldehyde. Compound 48/80 is known to cause severe itch because it specifically activates and degranulates mast cells and thus release histamine. Thus, compound 48/80 is often used as a pruritogenic substance. However, the mechanism underlying its mast cell degranulation is not well understood. Thus, we aimed to determine ion channels that are activated specifically by compound 48/80. To do that, a rat basophilic leukemia cell line (RBL-2H3) was used as a mast cell model. As a result, application of compound 48/80 to RBL-2H3 cells evoked robust Ca2+ increase. The EC50 of compound 48/80 was about 100 ug/ml. This Ca2+ response is induced by the influx of Ca2+ from the outside cell because Ca2+-free bath solution failed to show the increase in intracellular Ca2+. The compound 48/80-induced Ca2+ was not blocked by ruthenium red, a TRP channel blocker. Surprisingly, The compound 48/80-induced Ca2+ was completely blocked by the application of 4,4'-diisothiocyano-2,2'-stilbenedisulfonic acid (DIDS), a Cl- channel blocker, suggesting the involvement of chloride channels. Thus, future study is directed to determine which Cl- channels are involved in the compound 48/80-induced Ca2+ signal in RBL-2H3 cells. The understanding of channels activated by compound 48/80 will lead to the detailed mechanisms underlying pathologic pruritus and may be useful for developing new anti-pruritic drugs.

Disclosures: B. Lee: None. **H. Chun:** None. **H. Kim:** None. **J. Wee:** None. **I. Choi:** None. **U. Oh:** None.

Poster

797. Mechanisms of Neuropathic Pain II

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 797.01/O46

Topic: D.08. Pain

Support: Intradepartmental fund, The University of Texas MD Anderson Cancer Center

Title: Rolipram ameliorates chemotherapy-induced neuropathic pain in rats by decreasing inflammatory cytokines in the dorsal root ganglia

Authors: S. KIM, H. KIM, H. LEE, S. ABDI;
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Abstract: Chemotherapy agents including taxanes, vinca alkaloids, and platinum complexes produce peripheral neuropathic pain which is a dose-limiting side effect. We previously reported that rolipram (ROL) ameliorates paclitaxel (PAC)-induced neuropathic pain in rats. The purpose of this study was to investigate the effect of ROL on PAC-induced inflammatory cytokines in dorsal root ganglia (DRGs). PAC (2 mg/kg on days 0, 2, 4, 6) or vehicle (4% dimethyl sulfoxide and 4% Tween 80 in saline) was intraperitoneally injected in adult male Sprague-Dawley rats. ROL treated rats received intraperitoneal injection of 3 mg/kg of ROL on PAC-injected rats and then the DRGs were dissected at 1 hour after ROL injection. The L1-6 DRGs were dissected, homogenized in RIPA lysis buffer, separated in SDS polyacrylamide gens and then transferred to polyvinylidene fluoride membrane. For detections, blots were incubated with the primary antibody to phosphorylated NFκB (p- NFκB), IL-1β, TNF-α, and GAPDH, respectively and then incubated with the horseradish peroxidase-conjugated secondary antibody. The immunoblots were detected by a chemiluminescence detection system and normalized to GAPDH. Equal protein loading was performed using GAPDH expression as a control. PAC significantly increased the levels of p-NFκB, TNF-α and IL-1β in the DRGs at 14 days after the first PAC injection. Further, PAC-induced increase in p-NFκB, TNF-α, and IL-1β protein levels in the DRGs were decreased by ROL treatment. This result indicates that PAC increases the production of phosphorylated NFκB, TNF-α, and IL-1β in the DRGs and inhibition of PAC-induced inflammatory cytokines level in the DRGs may be the mechanisms underlying the analgesic effect of ROL for chemotherapy-induced neuropathic pain in rats.

Disclosures: S. Kim: None. **H. Kim:** None. **H. Lee:** None. **S. Abdi:** None.

Poster

797. Mechanisms of Neuropathic Pain II

Location: Hall A

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Topic: D.08. Pain

Title: Cortical reorganization in at-level central neuropathic pain

Authors: *G. H. BLUMENTHAL[1], M. R. DETLOFF[2], B. NANDAKUMAR[1], K. A. MOXON[1];
[1]Sch. of Biomed. Engineering, Sci. & Hlth. Systems,, Drexel Univ., Philadelphia, PA; [2]Dept. of Neurobio. & Anatomy, Spinal Cord Res. Ctr., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: While the intensity of chronic neuropathic pain (CNP) has been directly associated with the degree of reorganization in the somatosensory cortex (S1), many of these studies have focused on peripheral nerve injury and deafferentation in which the cortical representations surrounding the painful, deafferented regions expand. After spinal cord injury (SCI), similar reorganizational patterns have been seen in patients experiencing below-level pain, where representations neighboring the deafferented region display significant reorganization. It is unlikely that the patterns of S1 reorganization in SCI patients experiencing at-level pain are similar due to the extent of intact afferent input originating from the painful area. We hypothesize that after SCI, development of at-level tactile allodynia will be associated with an expanded somatosensory representation of the painful area. To test this, a spinal cord contusion injury at vertebral level T10 in the female Sprague Dawley rat was used. Increased incidence of supra spinal behaviors such as vocalization and avoidance in response to tactile stimulation of the injured area was used to indicate at-level CNP. Animals were tested for 5 weeks following injury using a 26 gram Von Frey filament applied to 24 locations on the trunk area spanning two dermatome levels above and below T10. Animals were then separated into at-level allodynic and non-allodynic group based on their responses at week 5. Sensory mapping experiments were performed on both groups of animals as well as normal controls. A high impedance tungsten microelectrode was lowered through cortical layers I-IV in 10 locations spanning the hind limb, forelimb, and trunk cortices. For each neuron recorded, receptive fields to tactile stimulation of the entire body surface were recorded. For each cortical location, the proportion of cells responsive to trunk stimulation was calculated and comparisons were made between groups. Our results show that for at-level allodynic animals, cortical locations extending into the forelimb representation had a higher proportion of cells responsive to trunk stimuli when compared to both non-allodynic and normal animals. Expanding on these result, we would like to explore therapies which address this maladaptive plasticity in order to attenuate or prevent the development of CNP.

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Poster

797. Mechanisms of Neuropathic Pain II

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Support: Korea government (MSIP) Grant No. 2013R1A1A2074231

Korea government (MSIP) Grant No. 2013R1A2A2A01067248

Title: Molecular mechanisms of satellite glia-dependent spinal cord microglia activation in nerve injury-induced neuropathic pain

Authors: ***S. LEE**[1], H. LIM[2], H. LEE[1], K. NOH[1], B. YOU[1], J. OH[3], H. MOK[4], B. KIM[5], J.-S. PARK[3], K. KIM[4];
[2]Neurosci. and Physiol., [3]Chem., [1]Seoul Natl. Univ., Seoul, Korea, Republic of; [4]Applied Chem., Kyung Hee Univ., Yongin, Korea, Republic of; [5]Brain Sci. and Neurol., Ajou Univ., Suwon, Korea, Republic of

Abstract: Increasing evidence supports the notion that both microglia activation in spinal cord and satellite glial cell (SGC) activation in dorsal root ganglion (DRG) play important roles in the development of neuropathic pain after peripheral nerve injury, yet their relative contributions to neuropathic pain induction remain elusive. To address this issue, we generated SGC-specific ikkβ conditional knockout mice in which IKK/NF-κB-dependent proinflammatory SGC activation is abrogated. In these mice, nerve injury-induced proinflammatory gene expression and macrophage infiltration into the DRG were severely compromised. Likewise, nerve injury-induced spinal cord microglia activation and pain hypersensitivity were significantly attenuated in these mice compared to control mice. However, macrophages recruited into the DRG per se have minimal effects on spinal cord microglia activation suggesting a direct causal effect of SGC activation on spinal cord microglia activation. In an effort to elucidate the molecular mechanisms, we found that IKK/NF-κB-dependent SGC activation induced St3gal2 gene expression and subsequent ganglioside (GT1b) production in DRG neurons as well as in the spinal cord dorsal horn. Studies using St3gal2 knock-out mice indicated that the GT1b increase is required for the nerve injury-induced spinal cord microglia activation and pain hypersensitivity. Finally, GT1b induced pain-mediating gene expression in primary microglia via

directly activating toll-like receptor 2 (TLR2) *in vitro* and also activated spinal cord microglia *in vivo*. Taken together, our data uncovered a novel mechanism for spinal cord microglia activation after nerve injury; nerve injury-induced SGC activation leads to GT1b up-regulation at the central axon terminal of the sensory neurons, which in turn activates spinal cord microglia via TLR2.

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Poster

797. Mechanisms of Neuropathic Pain II

Location: Hall A

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Program#/Poster#: 797.04/P1

Topic: D.08. Pain

Title: Coupled activation of primary sensory neurons contributes to chronic pain

Authors: *Y. KIM, K. PARK, S. JILAFU, Q. ZHENG, L. HAN, Z. LI, C. GONG, L. YOUNG, S. HE, F. ZHOU, Y. GUAN, M. CATERINA, X. DONG;
Dept Neurosci, Johns Hopkins Univ. Sch. Med., Baltimore, MD

Abstract: Primary sensory neurons in the dorsal root ganglia (DRG) play an essential role in initiating pain by detecting painful stimuli in the periphery and sending signals to the spinal cord via their axons. Pathological conditions such as inflammation and nerve injury can sensitize DRG neurons, causing heightened pain sensitivity and often leading to chronic pain. Although the mechanisms of hypersensitivity of individual neuron have been extensively studied, how DRG neurons function at a populational level under physiological and pathological conditions is unclear due to the lack of proper tools. By specifically expressing a genetically-encoded Ca2+ indicator in almost all dorsal root ganglion (DRG) and trigeminal ganglion (TG) neurons in Pirt-GCaMP mice. Using this technique, we developed an *in vivo* live imaging technique which allowed us to simultaneously monitor the activation of >1,700 neurons/DRG in response to mechanical stimulation applied to the receptive field in live mice. Using this powerful technique, we revealed a striking neuronal coupling phenomenon that is adjacent neurons tend to activate together in mice with inflammation or nerve injury, which rarely happens in naïve animals. The coupled activation occurs among various sizes of neurons including small-diameter nociceptors and large-diameter low-threshold mechanoreceptors. The transferring of non-membrane permeable dye between coupled-activating neurons suggests that the coupled activation is likely due to non-diffusible cell-to-cell communication. Combining pharmacological and genetic

approaches with the imaging technique, we found the coupling phenomenon is mediated by the upregulation of gap junction in satellite glial cells surrounding DRG neurons after injury. Blocking gap junction significantly attenuates neuronal coupling in the DRG and mechanical hypersensitivity. Therefore, neuronal coupling represents a new form of neuronal plasticity in the DRG and by "hijacking" neighboring neurons through gap junction it contributes to pain hypersensitivity. Finally, this study creates a new way of characterizing the physiological properties and functions for developing new pain- or other modality-specific drug target for a treatment with few side effects.

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Poster

797. Mechanisms of Neuropathic Pain II

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Support: National Research Foundation of Korea grant 2008-0062282

National Research Foundation of Korea grant 2012M3A9B6055414

Title: Preemptive analgesia attenuates mechanical allodynia in rats with chronic constriction injury of infraorbital nerve

Authors: H. KIM[1], M. KIM[1], J. SON[1], J. JU[1], K. YANG[1], M. LEE[2], M. PARK[3], *D. K. AHN[1]; [1]Dentistry, Kyungpook Univ., Daegu, Korea, Republic of; [2]Dong-Eui Univ., Busan, Korea, Republic of; [3]Kyung-Woon Univ., Gumi, Korea, Republic of

Abstract: The purpose of present study is to examine effects of preemptive analgesia on the development of neuropathic pain. For this purpose, the mechanical allodynia has been evaluated in rats with chronic constriction injury of infraorbital nerve (ION-CCI) after perineural application of 2% QX-314 in the infraorbital nerve. The effects of MIP-1α antibody on anti-allodynic actions by QX-314-induced preemptive analgesia are also investigated. Experiments were carried out using male Sprague-Dawley rats weighing between 230 and 280 g. Under anesthesia, ION-CCI was performed. ION-CCI produced severe ipsilateral and contralateral mechanical allodynia. Perineural application of 2 % of QX-314 on time after ION-CCI reduced

neuropathic mechanical allodynia. Double application of QX-314 significantly attenuated development of mechanical allodynia compared to the single treatment with QX-314. Application of 2% QX-314, when pain is already established, did not affect neuropathic mechanical allodynia. Co-administration of MIP-1α antibody and QX-314 potentiated anti-allodynic effects of QX-314 as a dose-dependent manner. Application of QX-314 did not affect extravasated Evans' blue dye concentration and the number of ATF3-positive cells produced by ION-CCI. The up-regulated p-p38 expression is co-localized with NeuN, a neuronal cell marker. The application of QX-314 reduced the up-regulated GFAP and p-p38 expression produced by ION-CCI in the trigeminal ganglion. These results suggest that QX314-induced long lasting preemptive analgesia produces inhibition of development of neuropathic pain through a regulation of the satellite glial cells and neuronal p-p38 expression in the trigeminal ganglion. Importantly, these results provide a potential preemptive therapeutic strategy for the treatment of neuropathic pain following nerve injury.

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Poster

797. Mechanisms of Neuropathic Pain II

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Topic: D.08. Pain

Support: DOD grant

CCF neurology institute funding

Title: Dynamic changes of CCR2+ monocyte and Cx3CR1+ microglia in a mouse model of neuropathic pain

Authors: ***L. LIU**, Z. HUA, H. WU, J. CHENG;
LRI, Cleveland Clin., Cleveland, OH

Abstract: Backgrounds: Neuropathic pain affects millions of Americans and can be severely debilitating. It has been recognized that the development of neuropathic pain in response to peripheral nerve injury in a large part depends on activation of microglia located in the dorsal horn of the spinal cord. Two chemokines (CCL2 and CCL21), which are expressed in injured neurons, have been indicated in the signaling pathways between injured neurons and microglia.

However, it remains to be elucidated that how a peripheral nerve injury initiates microglia responses in the dorsal horn of the spinal cord as there is no evidence that microglia express CCR2. We are particularly interested in the role of CCR2 expressing monocytes in this process and specifically investigated the dynamic distribution of monocytes from the circulation in the sciatic nerve, the dorsal root ganglia (DRG), and the spinal cord in response to chronic constriction injury (CCI) of the sciatic nerve in mice. We hypothesized that CCR2 expressing monocytes are attracted by CCL2 released from the injured DRG neurons to the spinal cord and DRG in response to CCI of the sciatic nerve in mice. We further hypothesized that CX3CR1 expressing microglia are activated in response to the nerve injury. **Methods:** With IACUC approval, CCI of the right sciatic nerve was induced by loose ligation on Cx3CR1GFP/+; CCR2RFP/+ transgenic mice. Sham-operated animals (sciatic nerve exposure without ligation) were used as controls. Mechanical allodynia was evaluated on day 0, day 7, day 14, day 21 and day 28. Mice were sacrificed and perfused at these time intervals. Samples of the sciatic nerve, DRG, and spinal cord of both sides were collected for immunohistochemistry examination to identify CCR2+ expressing monocytes and CX3CR1 expressing microglia. **Results**: CCI of the sciatic nerve induced a significant reduction of withdrawal thresholds to mechanical stimulation on post-injury day 7 through day 28. CCR2+ monocytes were identified in the sciatic nerve and DRG, but not in the spinal cord. An increase of CX3CR1 expression (activation of microglia) was found in the spinal cord dorsal horn ipsilateral to the CCI. The increase was noticeable in post-injury Day 3, peaked at Day 14, and waned at Day 28. **Conclusions**: We have demonstrated an infiltration of monocytes in the sciatic nerve and DRG, but not in the spinal cord, in response to the sciatic nerve injury. Further, we have shown a dynamic expression of CX3CR1 in the spinal cord, which is likely to be related to the mechanical allodynia. The link between monocyte infiltration and microglia activation remains to be established and is being actively investigated.

Disclosures: **L. Liu:** None. **Z. Hua:** None. **H. Wu:** None. **J. Cheng:** None.

Poster

797. Mechanisms of Neuropathic Pain II

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Topic: D.08. Pain

Support: Pfizer Canada

Alan Edwards Foundation Postdoctoral Fellowship

Title: Changes in DNA methylation in the rodent prefrontal cortex in chronic neuropathic pain: effect of S-Adenosylmethionine (SAM) on pain behaviors and epigenetic process

Authors: *S. GREGOIRE[1,2], R. MASSART[3,1], M. MILLECAMPS[2,1], S. DYMOV[3,1], S. DO CARMO[3,1], A. CUELLO[3,1], M. SZYF[3,1], L. STONE[2,1];
[2]Dent., [3]Pharmacol. and Therapeut., [1]McGill Univ., Montreal, QC, Canada

Abstract: Despite considerable advances in understanding mechanisms involved in chronic pain, it remains difficult to treat effectively. Co-morbid conditions including anxiety, depression and cognitive impairment further impact quality of life. Chronic pain is associated with reversible changes in brain anatomy and function and with long-term alterations in gene expression. One mechanism underlying stable, long-term programming of gene expression is DNA methylation, a dynamic process that responds to environment and experiences throughout the life cycle. We previously reported a decrease in global DNA methylation in the prefrontal cortex (PFC) in a rodent model of chronic neuropathic pain (Spared Nerve Injury, SNI). However, neither the identity of individual differentially regulated genes nor the effect of increasing global methylation on pain, mood and cognitive have been examined. In the current study, DNA methylation was first explored in SNI and control animals in rat PFC nine months following nerve injury. Genome-wide DNA methylation analysis revealed difference in the DNA methylation landscape in the brain at over 12,000 individual genes. DNA methylation of numerous individual genes the PFC showed robust correlation with pain sensitivity (von Frey test), including genes involved in pain modulation (e.g. opioidergic, dopaminergic or glutamatergic signaling) as well as in epigenetic processes (e.g. DNA methyltransferases). This first study supports the plausibility of DNA methylation involvement in chronic pain. In the second study, the effect of modulating DNA methylation on pain-related behaviors was assessed. Animals with nerve injury and sham surgery controls were treated with the methyl donor S-adenosylmethionine (SAM). SAM serves an important biological function as a methyl donor for DNA methyltransferases (DNMTs) in a multitude of cellular methylation reactions in all organisms. Three months following nerve injury, SAM or saline solution was given orally for four months and the effect of SAM on sensitivity to mechanical and cold stimuli, anxiety/depressive-like behaviors, pain avoidance and cognitive ability were measured. SAM attenuated SNI-induced mechanical hypersensitivity and pain avoidance in SNI mice. SAM had no effect on cold sensitivity and on anxiety/depressive-like behaviors but reversed the SNI-induced cognitive impairment in the novel object recognition test. In summary, chronic neuropathic pain results in changes in the DNA methylation of thousands of individual genes in the rodent PFC and the repeated administration of a methyl donor attenuated sensory and cognitive symptoms associated with nerve injury.

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Poster

797. Mechanisms of Neuropathic Pain II

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Topic: D.08. Pain

Support: 2012R1A3A1050385

Title: Ongoing synthesis of synaptic proteins supports synaptic remodeling and behavioral changes induced by nerve injury

Authors: *J.-H. CHOI[1], J.-I. KIM[1], H.-G. KO[1], X. LI[2], C.-S. LIM[1], S.-E. SIM[1], J. SHIM[1], S. J. KANG[1], T.-H. CHOI[1], D.-I. PARK[3], J. DO[1], G. L. COLLINGRIDGE[4], C. W. TURCK[3], M. ZHUO[2], B.-K. KAANG[1];
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Abstract: Sensory experience induces reorganization of synaptic structure and functions in the brain. Many studies have demonstrated dynamic changes such as spine formation, elimination, and maturation of spine morphology in visual cortex, somatosensory cortex, and motor cortex following sensory experience or motor learning. However, mechanisms underlying synaptic remodeling induced and maintained by sensory inputs are poorly understood. Here we have found that constant sensory inputs through nerve injury induces increased synthesis of synaptic proteins in the anterior cingulate cortex, which in turn supports experience-dependent remodeling of synaptic structure, function and following behavioral changes. (J.-H. CHOI and J.-I. KIM both contributed equally to this work)

Disclosures: **J. Choi:** None. **J. Kim:** None. **H. Ko:** None. **X. Li:** None. **C. Lim:** None. **S. Sim:** None. **J. Shim:** None. **S.J. Kang:** None. **T. Choi:** None. **D. Park:** None. **J. Do:** None. **G.L. Collingridge:** None. **C.W. Turck:** None. **M. Zhuo:** None. **B. Kaang:** None.

Poster

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National Science Council-100-2321-B-037-001

Title: Suppression of GSKIP expression in mice enhance CCI-dependent neuropathic pain through GSK3β-mediated Drp1-associated mitochondrial dysfunction

Authors: *A.-K. CHOU[1], M.-C. HONG[1], Y.-R. HONG[2];
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Abstract: Neuropathic pain is one of prevalent chronic pain, estimating to affect one-fifth of people in the world. Previous studies revealed peripheral neuropathy often induces ROS production and mitochondrial dysfunction. However, the antioxidants are often tended to have only a modest therapeutic effect in neuropathic pain due to the precisely pathogenesis mechanisms remain unclear. Recently, Drp1 and GSK3 inhibitors have been shown the therapeutic effects to alleviate symptoms of neuropathic pain by reducing ROS production and mitochondrial fragmentation. Accumulation of cytoplasmic β-catenin and cyclin D1 expression which somehow contributes to the persistence of neuropathic pain can be suppressed by blockage of WNT pathway. We previously identified a small AKAP, GSKIP (GSK3β interaction protein), which not only negatively regulates GSK3 to mediate Drp1 GTPase activity but also associates with β-catenin accumulation to promote cyclin D1 expression under RA stimulation, implicating that GSKIP is an inhibitor of GSK3. Furthermore, our results in SH-SY5Y cells showed that GSKIP tethering GSK3β to induce the phosphorylation of Drp1 Ser637 by cAMP-driven PKA across PKA/GSKIP/GSK3/Drp1 axis, indicating GSKIP may play a role to ameliorate mitochondria fragmentation and mitochondria-derived ROS production. Indeed, the level of pGSK3β S9 phosphorylation is reduced in heterozygous GSKIP KO embryo and almost disappeared in homozygous GSKIP KO embryo. After CCI nerve injury, the development of thermal hyperalgesia after 14 days was enhanced in the heterozygous GSKIP KO mice. Overall, all of the results suggested that depletion or decreasing of GSKIP expression in mice can lead to an intensely neuropathic pain at the late stage. Administration of GSKIP-specific peptides may provide a better therapeutic effect to reduce peripheral neuropathic pain.

Disclosures: A. Chou: None. **M. Hong:** None. **Y. Hong:** None.

Poster

797. Mechanisms of Neuropathic Pain II

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NSFC grant 81200859

Title: BDNF-mediated projection-specific modulation of depression and pain: Focus on dopaminergic neurons in VTA

Authors: *D. LIU, Q.-Q. TANG, C. YIN, H. LIU, S.-P. SONG, Y.-Q. LI, Z.-Q. PAN, H.-R. WANG, X.-Y. HONG, Y. LIU, X.-Y. GUO, X.-N. YANG, H.-L. DING, H. ZHANG, J.-L. CAO;
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Abstract: Preclinical and clinicalbrain functional imaging studies have indicated that mesolimbic reward circuitry might play the critical roles in regulation of both depression and pain. The great functional heterogeneity of dopaminergic (DA) neurons in ventral tegmental area (VTA), a critical brain structure of mesolimbic reward circuitry, is the base of its extensive effect on regulating different behavioral responses in depression and pain. However, how VTA DA neuronal heterogeneity regulating depression and pain behaviors remains unknown. Mice treated with 5 consecutive weeks of CUMS showed depressive behavioral phenotypes, but no significant thermal pain behavior was found. Compared to control group, the firing rates in prefrontal cortex (PFC) projecting VTA (VTA-PFC) DA neurons were decreased in CUMS-treated mice. In nucleus accumbens (NAc) projecting VTA (VTA-NAc) DA neurons, however, no significant alterations of the firing rates were observed subsequent to CUMS. Both VTA-PFC and VTA-NAc DA neurons showed the elevated response to morphine in CUMS mice. The dosage of morphine used in present study doesn't change VTA DA excitability in control mice. Behavioral tests showed that microinjection of morphine in VTA relieved the depressive symptoms, which was accompanied with thermal pain hyperalgesia. Depression relief effect in CUMS mice by micro-injection of morphine in VTA could be mimicked by micro-injection of exogenous BDNF and be blunted by micro-injection of TrkB-Fc in mPFC, but not in NAc. Thermal hyperalgesia induced by micro-injection of morphine in VTA in CUMS mice by could be mimicked by micro-injection of exogenous BDNF and be blunted by micro-injection of TrkB-Fc in NAc, but not in

mPFC. CUMS decreased BNDF expression in mPFC, not in NAc, but increased BDNF expression was observed in both after micro-injection of morphine in VTA. Our results demonstrated a novel mechanism of BDNF-mediated projection-specific modulation of depression and pain by mesolimbic reward system.

Disclosures: **D. Liu:** None. **Q. Tang:** None. **C. Yin:** None. **H. Liu:** None. **S. Song:** None. **Y. Li:** None. **Z. Pan:** None. **H. Wang:** None. **X. Hong:** None. **Y. Liu:** None. **X. Guo:** None. **X. Yang:** None. **H. Ding:** None. **H. Zhang:** None. **J. Cao:** None.

Poster

797. Mechanisms of Neuropathic Pain II

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Topic: D.08. Pain

Support: Grants-in-Aid for Research Activity Start-up

Grant-in-Aid for Challenging Exploratory Research

Title: Study of the expression of neuropeptide pituitary adenylate-cyclase activating polypeptide (PACAP) in neuropathic pain mice by psychological stress

Authors: ***Y. SHUDO**, M. SHIMOJO, M. FUKUNAGA;
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Abstract: It has been widely recognized that physical stress can cause the physiological, biochemical, and behavioral changes, leading to depressive illness. Stress has recently been reported to be involved in the pathogenesis of neuropathic pain and psychiatric disorders. Neuropathic pain is one of the most common type of intractable pain which control is difficult and has an impact on psychological and social factors. It was reported that neuropeptide pituitary adenylate-cyclase activating polypeptide (PACAP) is required for the development of spinal sensitization and induction of neuropathic pain. PACAP is distributed widely in dorsal root ganglia (DRG) and increases after nerve injury in neuropathic pain model. We previously reported that expression of PACAP in DRG is regulated by RE1-silencing transcription factor (REST) through alternative splicing of REST in neuropathic pain model mice. (Shudo et al., under review 2015). In this study, the mice (6 weeks) were used for neuropathic pain model and after 1 week of surgery then mice were restrained for 2 hours daily for 6 days to stimulate the psychological stress. Degree of stress was assessed by measuring cortisol in blood by specific

ELISA. The effect of the restraint stress on mechanical allodynia was assessed in chronic constriction nerve injury (CCI) neuropathic pain model mice. The nerve injury-induced mechanical allodynia was evaluated by using von Frey test. DRGs were obtained in model mice and the expression of genes were analyzed with specific primers by quantitative RT-PCR. As a result, psychological stress induced nerve injury-induced mechanical allodynia and the expression of PACAP in DRG in CCI model mice. It was suggested that stress exacerbates neuropathic pain and induced the expression of PACAP. To address the mechanism of stress-induced pain and the expression of PACAP, we have been currently analyzing the expression of other neuropathic pain-related genes.

Disclosures: **Y. Shudo:** None. **M. Shimojo:** None. **M. Fukunaga:** None.

Poster

797. Mechanisms of Neuropathic Pain II

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Support: Kirby pilot funding Boston Children's Hospital

Title: Cancer chemotherapy-induced peripheral neuropathy phenotypic screen

Authors: ***B. SINGH**, E. BUTTERMORE, L. BARRETT, C. WOOLF;
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Abstract: Patients undergoing chemotherapy for cancer often suffer from dose-limiting side effects, including painful peripheral neuropathy, which occurs in 30-60% of patients. Multiple different classes of chemotherapeutic agents, such as vinca alkaloids, platinum based, taxanes and a newer class, proteasome inhibitors can cause chemotherapy-induced peripheral neuropathy (CIPN). CIPN can result in loss of sensation, reduced epidermal innervation, and neuropathic pain, which can be transient or persist long after treatment has ceased. Unfortunately, there are no treatments available to prevent or improve neuropathy, and the associated neuropathic pain is poorly controlled with currently available analgesics. Furthermore, there is no consensus on the mechanism(s) responsible for the induction of neuropathy in CIPN-treated patients, nor a robust *in vitro* assay to detect the risk of development of neuropathy. We have developed two high throughput phenotypic screens specifically designed to examine CIPN induced neural toxicity. The primary screen will utilize mouse primary sensory neurons and a secondary screen will utilize human fibroblast-derived nociceptor neurons, which are derived using a

transdifferentiation approach (Wainger et al., Nature Neuroscience, 2015). The purpose of utilizing mouse and human neurons is two-fold; first, to detect species-specific differences and second, to allow us to translate the findings into *in vivo* work in mice, as well as potential clinical trials. We use neurite outgrowth as a measure of neurotoxicity, and find that both mouse primary dorsal root ganglia (DRG) sensory neurons and human fibroblast-derived sensory neurons respond to Paclitaxel and Bortezomib with dose-dependent decreases in neurite outgrowth. We are evaluating full dose responses for different classes of chemotherapeutic agents using a Cellomics Arrayscan XTI system to image and analyze neurite outgrowth. Once we have these mouse and human toxicity profiles, we will begin to explore the mechanisms responsible for the neurotoxicity and assess if we can identify which patients are at risk of developing CIPN by making iPSC lines and assessing if *in vitro* toxicity of derived patient sensory neurons correlates with clinical neuropathy and pain response.

Disclosures: B. Singh: None. **E. Buttermore:** None. **L. Barrett:** None. **C. Woolf:** None.

Poster

797. Mechanisms of Neuropathic Pain II

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Topic: D.08. Pain

Title: Characterizing the effects of prenatal alcohol exposure on glial-immune responses during chronic neuropathic pain

Authors: *J. SANCHEZ[1,2], A. G. VANDERWALL[2,3], M. S. SUN[2], S. DAVIES[2], T. ANDERSON[3], J. P. NORENBERG[3], D. D. SAVAGE[2,4,5], E. D. MILLIGAN[2,3]; [2]Neurosci., [3]Anesthesiol. and Critical Care, [4]Psychology, [5]Pediatrics, [1]Univ. of New Mexico, Albuquerque, NM

Abstract: Introduction: Neuropathic pain occurs as a consequence of abnormal neuronal signaling. Immune signaling molecules such as cytokines and chemokines derived from activated non-neuronal spinal glial cells (astrocytes and microglia) are critical in mediating the development and maintenance of peripheral neuropathic pain. The pro-inflammatory cytokine, interleukin-1 (IL-1β), and the chemokine, CCL2, mediate neuropathic pain such as mechanical allodynia, which is painful sensitization to light touch. Clinically, individuals with altered immune function leading to peripheral nerve damage experience chronic pathological pain. Additionally, reports indicate that people with fetal alcohol spectrum disorder (FASD) may have aberrant immune responses. Studies in animal models of prenatal alcohol exposure (PAE)

demonstrate that PAE rats stimulated with antigen-specific adjuvants trigger greater disease severity with a protracted time course compared to controls. Therefore, we examined whether PAE resulted in heightened spinal glial activation, cytokine/chemokine levels, peripheral immune cell trafficking into lumbar spinal regions, and greater allodynia compared to non-PAE controls following sciatic nerve damage in adult rats. Methods: Either saccharin controls (Sac) or PAE rats underwent unilateral sciatic nerve chronic constriction injury (CCI) or sham surgery following baseline (BL) behavioral assessment for light mechanical touch (von Frey test), with behavioral re-assessment at 3 and 10 days later. On Day 10 post-CCI, all rats were anesthetized and whole animal nanoSPECT/CT™ imaging was performed. Intravenous indium-111-labeled peritoneal leukocytes (^{111}In-Leuk), collected from same-stock donor rats, were monitored for trafficking into spinal column regions. Following imaging, anesthetized rats underwent transcardial saline and paraformaldehyde perfusion, with subsequent dorsal lumbar (L4-L5) spinal tissue collection and processing for immunohistochemical (IHC) detection of astrocyte & microglial activation. Results: Adult rats with PAE and CCI revealed heightened allodynia, greater spinal lumbar joint (intervertebral discs) leukocyte accumulation, and heightened astrocyte activation compared to sham and/or Sac controls. Ongoing IHC studies are characterizing dorsal lumbar spinal microglial activation, IL-1β, CCL2, CCR2, β_2-Integrins (LFA-1 & MAC-1) and interleukin-10. These results indicate that PAE causes long-lasting alterations in neuroimmune responsiveness that heightens chronic pathological pain.

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Poster

797. Mechanisms of Neuropathic Pain II

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NIH Grant DE02274

Title: Alterations in layer 5 pyramidal neurons of prelimbic medial prefrontal cortex in a rat model of neuropathic pain

Authors: *C. J. KELLY, M. MARTINA;
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Abstract: Chronic neuropathic pain is a complex and debilitating condition for which effective treatments are often unavailable. In addition to the sensory component, neuropathic pain is often accompanied by cognitive symptoms such as depression, anxiety, and deficits in decision making and working memory. To understand how pain and cognition interact, the medial prefrontal cortex (mPFC) is a particularly interesting region to explore due to its role in integrating sensory and emotional information and its important role in working memory. Here, we examine pyramidal neurons in layer 5 of prelimbic mPFC in the spared nerve injury (SNI) rat model of neuropathic pain. We find that dendritic length and branching are decreased in SNI, specifically in the proximal apical dendritic region (the apical dendrite excluding the tuft). There is a corresponding slight reduction of frequency of mEPSC events. This reduction appears selective for smaller events, consistent with the idea that more distal synapses are particularly affected while basal dendrites near the soma are unaffected. The evoked synaptic current at a holding potential of -70 mV is also reduced in SNI animals. Somewhat unexpectedly, however, we did not detect any impairment in LTP in these neurons. Due to the localized morphological changes and the large variability in evoked responses, we hypothesize that changes in this region are input-specific.

Disclosures: **C.J. Kelly:** None. **M. Martina:** None.

Poster

797. Mechanisms of Neuropathic Pain II

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NIH R01DA034749

Title: Antisense oligodeoxynucleotides CPEB suppresses neuropathic pain induced by HIV gp120 combined with ddC through ROS and CBP in Rats

Authors: *T. IIDA, S. LIU, H. YI, W. HUANG, D. LUBARSKY, S. HAO;
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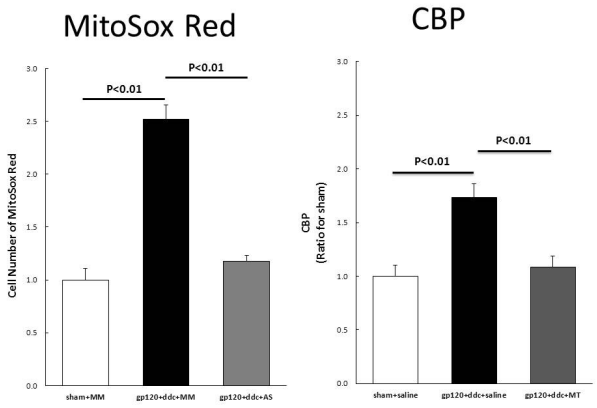
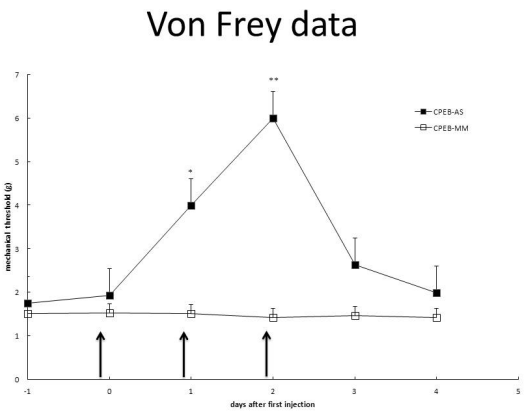
Abstract: Patients with HIV infection have numerous complications including neurological disorders. HIV-associated sensory neuropathy is one of the most common form of neuropathies. Both HIV infection-related distal sensory polyneuropathy and antiretroviral toxic neuropathy contribute HIV-related painful sensory neuropathy. The exact molecular mechanisms of HIV-associated neuropathic pain are still elusive. Cytoplasmic-element-binding (CPEB) protein is a sequence-specific RNA-binding protein that regulates protein translation involved in inflammation. Our previous studies showed that ROS was involved in the HIV-related pain. The role of cyclic-AMP response element-binding protein (CREB)-CREB binding protein (CBP) transcription factor in HIV neuropathic pain is not clear. In this study, we tested whether CPEB, ROS or CBP played a role in a rat pain model of HIV gp120 combined with anti-retroviral therapy. Neuropathic pain was induced by HIV coat protein gp120 application combined ddC (an anti-HIV drug). Mechanical threshold was measured using Von Frey fibers. Intrathecal antisense oligodeoxynucleotides (AS ODN) against CPEB, and mitochondrial superoxide scavenger Mito-Tempol reduced neuropathic pain. CPEB-AS treatment suppressed mitochondrial oxidative stress. Mito-Tempol reduced the expression of CBP in the spinal dorsal horn in the HIV pain model. Our results suggest spinal CPEB play a role in a rat pain model of HIV gp120 combined with anti-retroviral therapy through ROS and CBP.





Disclosures: **T. Iida:** None. **S. Liu:** None. **H. Yi:** None. **W. Huang:** None. **D. Lubarsky:** None. **S. Hao:** None.

Poster

797. Mechanisms of Neuropathic Pain II

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FRQS

Title: A role for noradrenergic modulation in neuropathy-induced hyperexcitability of pyramidal neurons in the medial prefrontal cortex

Authors: *S. CORDEIRO MATOS[1,2], Z. ZHANG[1,2], G. LONGO[3,2], A. RIBEIRO-DA-SILVA[3,2], P. SEGUELA[1,2];
[1]Montreal Neurolog. Institute, McGill Univ., Montreal, QC, Canada; [2]Alan Edwards Ctr. for Res. on Pain, Montreal, QC, Canada; [3]Pharmacol. and Therapeut., McGill Univ., Montreal, QC, Canada

Abstract: It is well established that hyperpolarization-activated cyclic nucleotide-gated (HCN) channels regulate a variety of critical neuronal properties. Moreover, cationic currents mediated by HCN channels (Ih) play a role in peripheral pain pathways by facilitating ectopic firing and hyperexcitability. Consistently, mice in which HCN2 channels were selectively deleted in

Nav1.8-positive DRG nociceptors showed no neuropathic pain in response to mechanical and thermal stimuli. However, little is known regarding the role of Ih in supraspinal pain pathways. The medial prefrontal cortex (mPFC) is involved in affective aspects of pain and exhibits high HCN channel expression. Using the rat spared nerve injury (SNI) model of chronic neuropathic pain and whole-cell patch-clamp recordings in layer II/III pyramidal neurons of the mPFC, we observed a hyperpolarizing shift in the voltage-dependent activation of HCN channels in contralateral SNI neurons. Consistently, SNI neurons exhibited increased input resistance and excitability compared to sham neurons. However, the amplitude and density of maximal Ih were not significantly different between both groups. We previously observed that HCN channels modulate mGluR5-mediated persistent firing (PF), a cellular substrate for working memory, in layer II/III pyramidal neurons of the mPFC and that norepinephrine enhances PF via postsynaptic alpha-2 adrenoceptor-mediated HCN channel inhibition. Interestingly, subthreshold doses of the group 1 mGluR agonist DHPG evoked PF in SNI but not sham prefrontal neurons. Hence, this phenomenon may contribute to enhanced attention to pain and/or pain-related mnemonic processing. Furthermore, application of bromo-cAMP shifts the activation curve of HCN channels to more depolarized potentials in SNI neurons whereas application of the alpha-2 agonist clonidine induces a similar hyperpolarizing shift in the voltage-dependent activation of HCN channels as seen in SNI conditions. Interestingly, we further observed an increased density of noradrenergic fibers in the mPFC of SNI rats. These data suggest that noradrenergic modulation plays an important role in the HCN channel dysfunction observed in SNI neurons. Acute mPFC infusion experiments to investigate the behavioral consequences of altering cAMP levels or blocking HCN channels directly in sham and SNI rats are currently on-going.

Disclosures: **S. Cordeiro Matos:** None. **Z. Zhang:** None. **G. Longo:** None. **A. Ribeiro-da-Silva:** None. **P. Seguela:** None.

Poster

797. Mechanisms of Neuropathic Pain II

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Support: DK105687

Title: The first translatable prediction biomarker of painful peripheral neuropathy

Authors: *M. I. NEMENOV[1,2], M. BACKONJA[3,1];
[1]Lasmed LLC, Mountain View, CA; [2]Anesthesia, Stanford Univ., Stanford, CA; [3]Neurol., Univ. of Wisconsin-Madison, Madison, WI

Abstract: Mechanisms of painful peripheral neuropathies (PPN) are still not well known and biomarkers are not available. Currently, there are no effective treatments or predictive biomarkers that would aid in preventing development of PPN. Recently, it was demonstrated that spontaneously active (SA) small diameter nociceptive C and Aδ fibers are a likely source of chemotherapy induced painful neuropathy (CIPN) in rodents and humans. Paradoxically, spontaneous activity of these C fibers is correlated with skin denervation and deficits in sensation in patients with chronic pain. In humans, the majority of SA fibers are subepidermal C mechano-insensitive fibers. Surface (contact, radiant or CO2 laser) heat stimulation as a method of testing small diameter fibers allows only for simultaneous activation of both superficially located Aδ and C fibers and does not allow for independent activation of fibers located deeper in the skin. Thus, there is an unmet medical need for a mechanism-based, reliable clinical biomarker for the risk for painful CIPN that would be translatable to, preclinical biomarkers for analgesic development. To address all of these deficiencies we developed a technique to selectively access Aδ and C fibers using diode laser fiber type selective stimulation (DLss). DLss radiation penetrates deep the in skin, homogeneously heats superficial and subepidermal skin layers, and allows access to deeply located SA C fibers in humans and rodents (Moeller-Betram et al., Pain Medicine 2013, Greffrath et al., Pain 2002). We tested patients with peripheral painful diabetic neuropathy and CIPN and found that, in spite of skin denervation, the intensity of response thresholds of C fibers was not increased compared to healthy subjects, as it would have when non-selective radiant, contact, or CO2 laser heat stimulation are applied. However, the intensity of thresholds for Aδ was increased compared to healthy subjects. Such results can be explained only because DLss activates sensitized SA C fibers located deep in the skin. We hypothesize that ratios between DLss intensity required for threshold stimulation of Aδ and C fibers could be a sensitive biomarker for early stage development of PPN and Aδ/C ratios change before pain symptoms begin. We find a significant difference when ratios between healthy subjects and patients with painful diabetic neuropathy and painful CIPN are compared. DLss is a noninvasive device that is appropriate for mechanisms based translational therapeutic development and for fast transition to the market. that would follow 510K guidelines.

Disclosures: **M.I. Nemenov:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); LasMed LLC. **M. Backonja:** None.

Poster

797. Mechanisms of Neuropathic Pain II

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Topic: D.08. Pain

Title: Neuropathic pain behavior is reversed with epoetin alpha: a pilot study in the NeuroDigm GEL(TM) model of neuropathic pain

Authors: ***M. R. HANNAMAN**[1], D. A. FITTS[2], J. L. BRYANT[3];
[1]NeuroDigm Corp, Colorado Springs, CO; [2]Univ. of Washington (ret.), Arlington, WA; [3]Univ. Of Maryland, Baltimore, MD

Abstract: INTRODUCTION: The biological physiology creating persistent neural pain after a soft tissue injury in man has not been studied. In order to create a physiological model of persistent neural pain without acute nerve injury the last stage of tissue healing, called tissue remodeling, was reproduced in this model creating a neural lesion. This neural site was then treated with a biologic. METHODS: 14 male rats from a prior study had a percutaneous perineural depot of GEL by the posterior tibial nerve. The GEL was created of tissue components and peptides and induced mechanical hyperalgesia (pinprick) for 4 months until end of study. After this experiment was over, the 14 GEL rats continued in a pilot study and received injections of epoetin alfa (EPO) 200 units in normal saline at the site of the original GEL procedure (n = 5), a subcutaneous EPO injection of 200 units in NS (n = 4), or EPO control (no injection, n = 5). Days 140 and 149 after the GEL injection were taken as baseline days and then EPO was injected in the EPO groups on day 152. Pinprick data were collected on days 152, 153, 154, 156, 159, and 160 (end of study). The resulting data were analyzed using a mixed model ANOVA with EPO injection group as the between subjects factor (3 groups) and days as one repeated measures factor (7 days) and side as a second repeated measures factor (left and right paws). RESULTS: The groups-by-days interaction was significant ($F(14, 77) = 8.208$, $p < .001$) indicating that the 3 groups in this pilot study (EPO at site, EPO Subcutaneous and Control) were the same on days before the treatment and different on days after the treatment. EPO subcutaneous had no effect. EPO at the site in 5 rats significantly reduced paw withdrawals in response to pinprick on 5 test days over 7 days to the same extent on the right and left sides ($p < .001$). CONCLUSION: The targeted application of epoetin alfa decreased for 7 days the pain behaviors that had persisted for 4 months. The targeted delivery of a biologic, such as epoetin alpha, near a neural lesion long after a soft tissue injury may be able to reverse neuropathic pain behaviors.

Disclosures: **M.R. Hannaman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroDigm Corp. **D.A. Fitts:** None. **J.L. Bryant:** None.

Poster

797. Mechanisms of Neuropathic Pain II

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Topic: D.08. Pain

Support: DA037673

Title: Impact of genetic reduction of NMNAT2 on chemotherapy-induced losses in cell viability *in vitro* and peripheral neuropathy *in vivo*

Authors: *R. SLIVICKI[1], Y. O. ALI[3], H.-C. LU[3], A. G. HOHMANN[2];
[1]Psychological and Brain Sci., [2]Indiana Univ., Bloomington, IN; [3]Dept. of Pediatrics, Baylor Col. of Med., Houston, TX

Abstract: Nicotinamide mononucleotide adenylyl transferases (NMNATs) are essential neuronal maintenance factors postulated to preserve neuronal function and protect neurons from axonal degeneration. NMNAT1 and the NMNAT associated Wallerian degeneration slow (Wlds) protein have been shown to protectt against chemotherapy insult *in vitro*. We hypothesized that NMNAT2 plays a protective role against neurotoxic effects of chemotherapeutic agents. We used *in vitro* and *in vivo* approaches to assess the impact of NMNAT2 reduction on cellular and physiological functions induced by treatment with a vinca alkaloid (vincristine) and a taxane-based (paclitaxel) chemotherapeutic agent. Primary cortical neurons prepared from NMNAT2 null embryos were rendered sensitive to degeneration triggered by either vincristine or paclitaxel treatment. NMNAT2 null mutant (NMNAT2-/-) mice die at birth whereas NMNAT2 heterozygous (NMNAT2+/-) mice exhibit a 50% reduction of normal NMNAT2 levels and survive to adulthood (Hicks et. al (2012) PLoS One. 7(10): p. e47869). Therefore, we examined the impact of NMNAT2 knockdown on the development and maintenance of chemotherapy-induced peripheral neuropathy induced by vincristine and paclitaxel in NMNAT2+/- and wild type (WT) mice. NMNAT2 (+/-) did not show altered responses during the development or the maintenance of either mechanical or cold allodynia induced by either vincristine or paclitaxel treatment compared to WT mice. Intradermal injection of capsaicin, the pungent ingredient in hot chili peppers, failed to unmask differences in nociceptive responses in NMNAT2+/- and WT mice rendered neuropathic by previous toxic challenges with paclitaxel. Moreover, no differences in motor behavior were detected between genotypes in the rotarod test. Our studies demonstrate that a 50% reduction of NMNAT2 is not sufficient to alter the development or maintenance of mechanical or cold allodynia induced by vincristine or paclitaxel treatment. Our studies do not preclude the possibility that complete knockout of NMNAT2 in a conditional

knockout animal would unmask a role for NMNAT2 in protection against detrimental effects of chemotherapeutic treatment.

Disclosures: **R. Slivicki:** None. **Y.O. Ali:** None. **H. Lu:** None. **A.G. Hohmann:** None.

Poster

797. Mechanisms of Neuropathic Pain II

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Program#/Poster#: 797.20/P17

Topic: D.08. Pain

Title: Role of microRNAs in oxaliplatin-induced neuropathy

Authors: *M. LÓPEZ GONZÁLEZ[1], S. BENQUET[1], F. VIANA[2], M. LANDRY[1], A. FAVEREAUX[1];
[1]Central mechanisms of pain sensitization, Interdisciplinary Inst. For Neurosci., Bordeaux Cedex, France; [2]Inst. de Neurociencias de Alicante, Univ. Miguel Hernández-CSIC, San Juan de Alicante, Spain

Abstract: Oxaliplatin is a reference chemotherapeutic drug for the treatment of gastrointestinal tract tumors that induces sensorial neuropathy in 70% of patients. Oxaliplatin induces acute side effects, such as cold hypersensitivity, dysesthesia and paraesthesia, and can evolve to a long-term neuropathy in a fraction of the affected patients (around 15-20%). The chronic side effects may be severe enough to prevent patients from performing daily life activities and include impaired sensation, sensory ataxia, and/or deficit in fine sensory-motor coordination. This can oblige physicians to limit the treatment with potentially useful anticancer drugs. We have developed a mouse model that mimics patients' symptoms with a single intraperitoneal injection of oxaliplatin. By behavioral studies such as dynamic weight bearing, we saw that impaired sensation and motor coordination appear three days after injection and last for several weeks. We also saw that oxaliplatin treatment reduces arborization of sensory neurons in culture in a dose-dependent manner. In order to characterize how the regulation of gene expression may play a role in oxaliplatin neuropathy, we have screened all miRNAs in mouse genome. We focused our attention to miRNAs having a role in axon guidance and neurite outgrowth. As a result, we highlighted miR-204, a miRNA that controls expression of two axon guidance molecules; PlexinA2, a receptor of Semaphorin6A, and DCC, a receptor of Netrin-1. Interaction of miR-204 and its targets was confirmed at molecular level. Furthermore, overexpression of miR-204 in dorsal root ganglia (DRG) neuron cultures reduces expression of PlexinA2 and DCC at RNA level, but also reduces length and extension of DRG neuron processes. Our hypothesis is that

oxaliplatin impairs sensitivity and motor coordination by a reduction in axon arborization of DRG neurons through an overexpression of miR-204 that reduces PlexinA2 and DCC expression.

Disclosures: M. López González: None. **S. Benquet:** None. **F. Viana:** None. **M. Landry:** None. **A. Favereaux:** None.

Poster

797. Mechanisms of Neuropathic Pain II

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 797.21/P18

Topic: D.08. Pain

Support: Intradepartmental fund, The University of Texas MD Anderson Cancer Center

Title: Pentoxifylline ameliorates chemotherapy-induced neuropathic pain in rats by decreasing inflammatory cytokines in the dorsal root ganglia

Authors: *H. KIM, S.-H. HWANG, H. LEE, S. ABDI;
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Abstract: Chemotherapy agents including taxanes, vinca alkaloids, and platinum complexes produce peripheral neuropathic pain which is a dose-limiting side effect. We previously reported that pentoxifylline (PTX) ameliorates paclitaxel (PAC)-induced neuropathic pain in rats. The purpose of this study was to investigate the effects of PTX on the PAC-induced inflammatory cytokines production in dorsal root ganglia (DRG). Adult male Sprague-Dawley rats received i.p. injection of Paclitaxel (2 mg/kg on days 0, 2, 4, 6) or vehicle (4% dimethyl sulfoxide and 4% Tween 80 in saline). PTX treated rats were administered with PTX, 100 mg/kg i.p. and then the L1-6 DRGs were obtained at 1 hour post injection. The DRGs were dissected, homogenized in RIPA lysis buffer, separated in SDS polyacrylamide gens and then transferred to polyvinylidene fluoride membrane. For detections, blots were incubated with the primary antibody to phosphorylated NFκB (p- NFκB), IL-1β, TNF-α, and GAPDH, respectively and then incubated with the horseradish peroxidase-conjugated secondary antibody. The immunoblots were detected by a chemiluminescence detection system and normalized to GAPDH. Equal protein loading was performed using GAPDH expression as a control. PAC significantly increased the levels of p-NFκB, TNF-α and IL-1β in the DRGs at 14 days after the first PAC injection. Further, PAC-induced increase in p-NFκB, TNF-α, and IL-1β protein levels in the DRGs was decreased by PTX treatment. This result indicates that PAC increases the production of phosphorylated NFκB,

TNF-α, and IL-1β in the DRGs and inhibition of PAC-induced inflammatory cytokines levels in the DRGs may be one of the mechanisms underlying the analgesic effect of PTX for chemotherapy-induced neuropathic pain in rats.

Disclosures: H. Kim: None. **S. Hwang:** None. **H. Lee:** None. **S. Abdi:** None.

Poster

797. Mechanisms of Neuropathic Pain II

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Topic: D.08. Pain

Support: KAKENHI C 25460729

KAKENHI B 25293137

Title: Localization of neuropathic pain-related protein, BEGAIN in the spinal dorsal horn

Authors: *T. KATANO[1], M. WATANABE[2], M. YAMAZAKI[3], M. ABE[3], I. YAO[4], K. SAKIMURA[3], S. ITO[1];
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Abstract: Neuropathic pain occurs by peripheral nerve injury and hyperalgesia or allodynia persists for a long time, which was attenuated in knock-in mouse with mutation of Tyr1472 to Phe of GluN2B (Y1472F KI). To clarify the mechanisms of neuropathic pain, we have analyzed the postynaptic density (PSD) fraction of spinal dorsal horn using Y1472F KI mouse after spared nerve injury (SNI) by proteomic approach and identified brain enriched guanyulate kinase associated protein (BEGAIN) as a novel neuropathic pain-related molecule in the neuropathic pain. A previous SfN meeting, we showed that mechanical allodynia by SNI, but not basal transmission, was significantly attenuated in BEGAIN knockout (KO) mice as compared to wild-type mice. Recently, we made BEGAIN specific antibody, and analyzed the localization of BEGAIN in the brain and spinal dorsal horn. BEGAIN was enriched in cerebellum, hippocampus and the dorsal horn, but not ventral horn, of the spinal cord. Moreover, BEGAIN was enriched in crude postsynaptic density (cPSD) in the hippocampus and spinal dorsal horn. The specific signal of BEGAIN was detected in layer II of spinal dorsal horn with IB4, a marker of layer IIi, and it was colocalized with PSD-95 and synaptophysin in the spinal dorsal horn, but

not GFAP-positive cell. Previous reports using BEGAIN KO mice and these results suggest that BEGAIN is involved in neuropathic pain in the spinal dorsal horn.

Disclosures: **T. Katano:** None. **M. Watanabe:** None. **M. Yamazaki:** None. **M. Abe:** None. **I. Yao:** None. **K. Sakimura:** None. **S. Ito:** None.

Poster

797. Mechanisms of Neuropathic Pain II

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Topic: D.08. Pain

Support: NIH NIGMS GM007205

PVA Research Foundation

Veterans Affairs Career Development Award

Title: Dendritic spine remodeling in lamina II dorsal horn sensory neurons after SCI

Authors: *L. W. PAPPALARDO, X. C. CAO, S. G. WAXMAN, A. M. TAN;
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Abstract: Neuropathic pain is a major complication of spinal cord injury (SCI) and despite aggressive efforts this type of pain is often refractory to available clinical treatment. Our previous work revealed a structure-function relationship between abnormal dendritic spine profiles on nociceptive sensory neurons in the deeper intermediate zone of the dorsal horn (laminae IV/V), and neuropathic pain following spinal cord injury (SCI). To extend these findings, we investigated whether abnormal dendritic spine remodeling occurs on superficial dorsal horn neurons located in the substantia gelatinosa, lamina II, after SCI. This region of the gray matter in the spinal cord is primarily involved in the integration of sensory stimuli that manifest as sensations of heat and pain. Although the literature has documented the presence of dendritic spines on lamina II neurons, their profiles have not been characterized following disease or injury. In this study, we analyzed dendritic spine morphometry and localization in adult rats one month after thoracic contusion SCI. In contrast to our previous published findings, the overall density of dendritic spines on sampled lamina II neurons did not increase. Instead, we observed a morphometric “switch”_ the density of thin-shaped dendritic spines decreased, whereas the density of mushroom-shaped spines concomitantly increased. Computer simulation data suggests that this switch from thin to mushroom spines (i.e., structures associated with

enhanced synaptic efficacy) in the superficial dorsal horn can contribute to nociceptive hyperexcitability. Intrathecal delivery of the Rac1-inhibitor, NSC23766, in animals with SCI significantly blocked the injury-induced switch from thin- to mushroom-shaped dendritic spines in lamina II. Taken together, these observations further support the link between abnormal dendritic spine remodeling and neuropathic pain after SCI, and the notion that dendritic spine dysgenesis can contribute to abnormal nociception.

Disclosures: L.W. Pappalardo: None. **X.C. Cao:** None. **S.G. Waxman:** None. **A.M. Tan:** None.

Poster

797. Mechanisms of Neuropathic Pain II

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Topic: D.08. Pain

Support: Grant-in-Aid for Scientific Research (23500468) from the Ministry of Education, Japan

Title: Characterization of the neuronal circuits in the spinal superficial dorsal horn: the application of multi-electrode array and cross-correlation analysis

Authors: Y. TAKEMURA, T. ASAKAWA, T. TERASHIMA, T. TAKASUSUKI, S. YAMAGUCHI, *Y. HORI;
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Abstract: Simultaneous recording of multi-neuronal activities using a multi-electrode array (MEA) system seems to be a powerful technique for characterizing neuronal interactions in local neural circuits. In the present experiment, we recorded spike activities simultaneously from multiple neurons in the spinal superficial dorsal horn (SDH) using the MEA system, and performed cross-correlation analysis of the spike trains in an attempt to characterize further the synaptic circuits underlying nociceptive processing in the spinal cord. Experiments were performed on 6- to 8-week-old male ICR mice. Under halothane anesthesia, the lumbar spinal cord was removed and transverse slices (400 μm in thickness) were made. The slices were placed into a recording chamber with the MEA (Multi Channel Systems, Germany). Electrodes were arranged 200 μm apart in an 8x8 pattern. The signals from the MEA electrodes were notch-filtered at 50 Hz to reduce power-line interference and sampled at 25 kHz. Only signals recorded from MEA electrodes located in the SDH were analyzed in the present experiments. In some

experiments, the sciatic nerve was partially ligated under halothane anesthesia according to Seltzer et al. (1990), and the development of mechanical allodynia was assessed by von Frey filaments. Off-line analysis of spike trains was conducted using DataView (Heitler, 2009). Single-unit spike trains were sorted from the recordings. Cross-correlograms between spontaneous spike trains of simultaneously recorded neurons in the SDH were constructed. The most frequent pattern observed in cross-correlograms was a flat histogram, indicating that there is no synaptic interaction between two neurons. However, a considerable number of neuron pairs exhibited significantly correlated activities. Among them were 1) common synaptic input to neuron pairs, which is evident from the presence of a central peak in the cross-correlogram; and 2) short-latency, monosynaptic excitatory and/or inhibitory interaction between neuron pairs, which is evident from the presence of a lagged peak and/or trough. Additionally, the incidence of significant cross-correlation between neural activities was increased in mice subjected to partial sciatic nerve ligation. The present observations seem to indicate that neurons in the SDH make excitatory and/or inhibitory synapses on the nearby neurons, and that synaptic connections among neurons in the SDH might change significantly after the development of neuropathic pain.

Disclosures: **Y. Takemura:** None. **T. Asakawa:** None. **T. Terashima:** None. **T. Takasusuki:** None. **S. Yamaguchi:** None. **Y. Hori:** None.

Poster

797. Mechanisms of Neuropathic Pain II

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Topic: D.08. Pain

Support: NIH DA034749

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Title: Mitochondrial fission is involved in the HIV gp120-related neuropathic pain in rats---a preliminary study

Authors: S. LIU, H. KANDA, C.-H. LIU, W. HUANG, D. A. LUBARSKY, *S. HAO;
Dept Anesthesiol., Univ. Miami, Miami, FL

Abstract: Human immunodeficiency virus (HIV) infection induces painful sensory neuropathy in HIV/IDS patients, but the exact molecular mechanisms of HIV neuropathic pain are elusive. Mitochondrial fusion and fission regulate cellular signaling, development, and mitochondrial homeostasis. In the present studies, we investigated the role of mitochondrial dynamin-related protein 1 (Drp1, a GTPase that mediates mitochondrial fission) in the HIV coat glycoprotein gp120-induced neuropathic pain state, and in gp120 with chronic morphine state. Neuropathic pain was induced by the application of recombinant HIV-1 envelope protein gp120 into the sciatic nerve. In the gp120 with chronic morphine pain state, rats received repeatedly intrathecal gp120 and chronic morphine. Mechanical threshold was tested using von Frey filaments. Mitochondrial superoxide in the spinal dorsal horn was measured using mitoSox (a mitochondrial superoxide indicator) profile cells. Intrathecal administration of either antisense oligodeoxynucleotide (ODN) against Drp1 or mitochondrial division inhibitor-1 (mdivi-1) decreased mechanical allodynia in the peripheral gp120 model. Moreover, both intrathecal Drp1 antisense ODN and mdivi-1 reversed the upregulation of mitochondrial superoxide in the spinal dorsal horn in the peripheral gp120 neuropathic pain state. In the neuropathic pain model of gp120 plus morphine, intrathecal mdivi-1 reversed mechanical allodynia either. We will discuss the different effects and the possible pathway. These data suggested mitochondrial division is involved in the HIV gp120-related neuropathic pain state.

Disclosures: S. Liu: None. **H. Kanda:** None. **C. Liu:** None. **W. Huang:** None. **D.A. Lubarsky:** None. **S. Hao:** None.

Poster

797. Mechanisms of Neuropathic Pain II

Location: Hall A

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Topic: D.08. Pain

Support: Strategic Research Initiative for IU Simon Cancer Center

NIH Grant RR025761

Title: Prolonged paclitaxel exposure modulates CGRP release induced by the activation of PKC in cultures derived from rat dorsal root ganglion

Authors: *L. DARBY, J. C. FEHRENBACHER;
Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: Paclitaxel is a microtubule stabilizing agent that is used in the treatment of solid tumor cancers such as breast, ovarian and lung cancer. Despite the efficacy of paclitaxel in cancer therapy regimens, patients are frequently forced to discontinue treatment due to the onset of peripheral neuropathy. Currently, no prophylactic or therapeutic treatments exist for peripheral neuropathy. This is, in large part, due to the lack of understanding regarding the basic mechanisms of action by which paclitaxel alters neuronal activity. A recent report demonstrates the activation of protein kinase C (PKC) following a 1-hr treatment of dorsal root ganglion (DRG) cultures with paclitaxel. Given that downregulation of PKC isozymes is pervasive upon persistent stimulation, we hypothesized that a prolonged exposure of sensory neurons to paclitaxel (48-72hr) would result in the downregulation of PKC and that this downregulation could underlie a loss of function observed in the sensory neurons, as we demonstrated previously. To address our hypothesis, we used an *in vitro* model of paclitaxel-induced neurotoxicity in primary cultures derived from rat DRG. The stimulated release of calcitonin gene-related peptide (CGRP) from these cultures was used to indicate activity of the peptidergic population of sensory neurons. In the absence of paclitaxel, activation of classic and novel PKC's with phorbol 12, 13 dibutyrate (PDBu; 10nM) enhanced CGRP release and this release was inhibited by **bisindolylmaleimide I** (1μM). After paclitaxel treatment, however, PDBu-stimulated release was attenuated in a concentration- and time- dependent manner, suggesting that paclitaxel decreases the function of one or more classic and/or novel PKC isozymes. Because PKCε has been proposed to play a major role in nociceptive signaling, we first examined expression of this isozyme. Paclitaxel decreased PKCε in a concentration- and time-dependent manner. Thus, the downregulation of PKCε is a possible mechanism by which paclitaxel attenuates neuronal activity of peptidergic sensory neurons. Further work is necessary to demonstrate a functional effect of PKCε activation and downregulation and to determine the role of other PKC isozymes in mediating the effects of paclitaxel on neuronal sensitivity.

Disclosures: L. Darby: None. **J.C. Fehrenbacher:** None.

Poster

797. Mechanisms of Neuropathic Pain II

Location: Hall A

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Topic: D.08. Pain

Support: NIH Grant RO1 NS031680

Title: Different types of reactive oxygen species are involved in cell type specific synaptic plasticity

Authors: *A. BITTAR, J. JUN, J. WANG, K. CHUNG, J. CHUNG;
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Abstract: It has been demonstrated that spinothalamic tract neurons (STTn) develop long term potentiation (LTP) while GABAergic interneurons (GABAn) develop long term depression (LTD) in response to the same intense afferent stimulation. Both LTP in STTn and LTD in GABAn seem to contribute to neuropathic pain. Recent study further showed that the induction of these two opposite synaptic plasticity is related to the different types of reactive oxygen species (ROS) that are generated within these two types of neurons. Our current hypothesis is that not only the induction but also the maintenance of the LTP in STTn and LTD in GABAn depend on superoxide and hydroxyl radicals, respectively. To test this hypothesis, the effects of specific ROS scavengers on the maintenance of STT/LTP and GABA/LTD and pain behavior are examined in the mouse model of spinal nerve ligation (SNL) neuropathic pain. Whole cell patch clamp recordings were used to test the effect of specific ROS scavengers on evoked excitatory postsynaptic currents (eEPSCs) in STTn and GABAn with afferent conditioning stimulations (ACS) to the dorsal root entry zone (DREZ) of the spinal cord. The effects of a general ROS scavenger PBN, superoxide scavenger TEMPOL (1 mM) and hydroxyl radical scavengers DMSO (100 mM) and DMTU (20 mM) were examined. The specific scavengers were applied to the recording chamber for 10 min either before (for induction) or 20 min after (for maintenance) the ACS. The effects of same scavengers on mechanical hypersensitivity of the foot were tested in SNL mice. TEMPOL blocked induction and reversed both STT/LTP and GABA/LTD maintenance as well as hypersensitivity in neuropathic mice. DMSO/DMTU reversed only GABA/LTD maintenance and partially inhibited hypersensitivity. Results indicate that superoxide radicals are involved in both STT/LTP and GABA/LTD induction and maintenance, whereas hydroxyl radicals contribute only to GABA/LTD. Furthermore, mechanical hypersensitivity in SNL mice is the result of the combination of STT/LTP and GABA/LTD in the dorsal horn.

Disclosures: **A. Bittar:** None. **J. Jun:** None. **J. Wang:** None. **K. Chung:** None. **J. Chung:** None.

Poster

797. Mechanisms of Neuropathic Pain II

Location: Hall A

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Topic: D.08. Pain

Title: The effect of partial sciatic nerve ligation on gabaergic function in the superficial dorsal horn: application of voltage-sensitive dye imaging system

Authors: *K. KANEKO[1], T. FUKUSHIMA[1], Y. NUMATA[2], T. TAKASUSUKI[2], S. YAMAGUCHI[2], Y. HORI[1];
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Abstract: The dysfunction of GABAergic inhibition in the superficial dorsal horn (SDH) causes the neuropathic pain, but the precise mechanisms are not fully elucidated. To better understand the pathological process of neuropathic pain, we investigated the effects of the partial sciatic nerve ligation (PSNL) on GABAA receptor function in the SDH by means of voltage-sensitive dye imaging. Under halothane anesthesia, 3-week-old male ICR mice were subjected to PSNL according to Seltzer et al. (1990). The mechanical allodynia was assessed with a von Frey filament. Control mice were sham-operated. The optical imaging experiments were performed one week after surgery. The spinal cord was removed under ketamine and xylazine anesthesia. The transverse spinal cord slices (400 μm in thickness) were prepared. The slices were stained with a voltage-sensitive dye Di-4-ANEPPS (Wako, Japan), then rinsed with Krebs solution. After staining, the slices were placed into the recording chamber on the microscope stage. The slices were routinely perfused with oxygenated Krebs solution containing tetrodotoxin. The Di-4-ANEPPS fluorescence was measured using the MiCAM2 optical imaging system (Brain Vision Inc., Japan). We analyzed fluorescence change in the SDH in response to bath-application of GABA. The bath-applied GABA increased Di-4-ANEPPS fluorescence in the SDH. This fluorescence increase was abolished by a GABAA receptor antagonist bicuculline. Thus, the fluorescence increase corresponds to membrane hyperpolarization by GABAA receptor activation. The amplitude of GABA-induced fluorescence increase was significantly smaller in PSNL mice than in control mice. The time course of the GABA response was significantly longer in PSNL mice than in control mice. The presently observed decreased amplitude of GABA-induced fluorescence change might be explained by down-regulation of GABAA receptors in the SDH or by a depolarizing shift in the chloride equilibrium potential of the SDH. The attenuated inhibitory response would lead to the initiation of neuropathic pain. It has been reported that the GABAA receptor subunit composition influences channel kinetics. The long time course of GABA response observed in PSNL mice seems to suggest that changes in the subunit composition are associated with PSNL-induced allodynia. Thus, we are currently performing real-time RT-PCR analysis for GABAA receptor subunits in PSNL mice. Such a experiments might provide a clue to the pathogenesis of neuropathic pain.

Disclosures: **K. Kaneko:** None. **T. Fukushima:** None. **Y. Numata:** None. **T. Takasusuki:** None. **S. Yamaguchi:** None. **Y. Hori:** None.

Poster

797. Mechanisms of Neuropathic Pain II

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Topic: D.08. Pain

Title: Minocycline prevents establishment of sensory hypersensitivity after a median nerve crush in rats

Authors: *S. SHAIKH, P. SHORTLAND, D. A. MAHNS;
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Abstract: Median nerve injury in the area of the axilla produces a bilateral hypersensitivity to mechanical and thermal (noxious heat and innocuous cold) stimuli that appears in the glabrous fore-paw within a week of the injury and persists for several weeks. The mechanisms underlying these phenomena remain to be elucidated. Nerve injury evokes a central glial reaction that is known to contribute to pain hypersensitivity. Drugs such as minocycline are known to affect microglial function and ameliorate pain sensitivity. This study has tested the hypothesis that minocycline can prevent the establishment of hypersensitivity after median nerve crush. Rats underwent unilateral median nerve injury or sham operation with naïve rats as controls. All animals were then randomized to receive either minocycline (40mg/kg i.p.) or a normal saline injection daily for 2 up to weeks. Researcher conducting the behavioural assessment randomized the mechanical and thermal tests and was blinded to the drug administration. Following behavioural assessment, animals were sacrificed and the C6-7 spinal cord and its corresponding ganglia were removed for immune-histochemical staining (microglia and astrocytes) or proteomic profiling of the dorsal horn of the spinal cord (2D gel electrophoresis using Coomassie brilliant blue). Consistent with our observation following median nerve transection a unilateral crush injury resulted in a 25-50% reduction in the withdrawal thresholds for tactile and noxious heating and the emergence of a marked intolerance to previously innocuous cooling. Minocycline successfully prevented the initiation and maintenance of behavioural hypersensitivity. Furthermore, comparison between vehicle treated (0.9% saline) and minocycline treated animals revealed a marked hypoalgesia in minocycline treated animals. Immuno- histochemical analysis of glial markers in the dorsal horn of the spinal cord (IBA-1 and GFAP) will define the relative contributions of neural versus non-neural contributions to hypersensitivity in this model. Furthermore, a non-selective proteomic profiling of the dorsal horn will reveal the up-regulated or down-regulated proteins centrally due to a peripheral nerve injury.

Disclosures: **S. Shaikh:** None. **P. Shortland:** None. **D.A. Mahns:** None.

Poster

798. Rhythmic Motor Patterns: Afferent and Descending Control

Location: Hall A

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Topic: D.11. Vertebrate and Invertebrate Rhythmic Motor Pattern Generation

Support: NSF IOS 1354932

DFG STE 937/9-1

Title: Recruitment of unimodal and multimodal neurons during sensory-induced motor pattern selection

Authors: *C. J. GOLDSMITH, W. STEIN;
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Abstract: Most motor systems can generate a variety of behaviors, including categorically different behaviors and variants of a single motor act within the same behavioral category. In many cases this multifunctionality results from dynamic adaptations of existing, highly interconnected neural circuits. This temporary restructuring of the motor circuits is controlled by descending extrinsic projections that alter motor activity in response to different sensory stimuli. The mechanisms by which motor pattern selection is controlled in different sensory conditions are largely unknown. We examined motor pattern control in the crustacean stomatogastric nervous system where several projection neurons in the paired commissural ganglia (CoGs; Stein, *J Comp Physiol A* 2009) are activated by sensory pathways and modulate downstream motor circuits. While selective stimulation of individual CoG projection neurons can elicit distinct versions of the gastric mill motor pattern (Nusbaum & Beenhakker, *Nature* 2002), typically several projection neurons are activated by sensory stimulation. Since it has been shown that some CoG neurons receive inputs from multiple sensory modalities, we hypothesize that distinct but overlapping sets of CoG neurons are activated by sensory pathways to determine the output activity of the motor circuits. Using voltage-sensitive dye imaging, we found that the population activity of CoG neurons differs during stimulation of 3 different sensory modalities that elicit distinct gastric mill rhythms. CoG neurons displayed a variety of rhythmic and non-rhythmic activity patterns. Sensory stimulation altered the activity of many CoG neurons and recruited some into the various motor patterns. Specifically, 39.6 % of visible cells in N= 6 CoGs began to exhibit rhythmic membrane potential oscillations that were timed with the gastric mill

rhythm. CoG activity patterns continued after stimulation and were recognizable for the duration of the motor pattern. Changes in CoG neuron activity were correlated with those in the gastric mill rhythm such that weaker CoG neuron activity corresponded to weaker motor patterns. CoG neuron activity returned to baseline when the gastric mill rhythm stopped. This was consistent across modalities. Our data also indicate a differential activation of CoG neurons across modalities: distinct, but overlapping pools of CoG neurons were recruited. In total, 25.1 ± 8.3 % of all gastric mill-timed neurons (N=6 CoGs) were multimodal and responded to at least two sensory modalities. Currently, we are analyzing the individual combinations of CoG neurons activated to better understand their contribution to motor pattern control.

Disclosures: C.J. Goldsmith: None. **W. Stein:** None.

Poster

798. Rhythmic Motor Patterns: Afferent and Descending Control

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Topic: D.11. Vertebrate and Invertebrate Rhythmic Motor Pattern Generation

Support: NSF Grant IOS 1354932

DFG Grant STE 937/9-1

Title: Topological identification of projection neurons controlling motor circuits

Authors: *R. FOLLMANN, C. J. GOLDSMITH, W. STEIN;
Sch. of Biol. Sci., Illinois State Univ., Normal, IL

Abstract: Modulatory projection neurons play a key role in the control of multifunctional central pattern generator circuits by selecting distinct output patterns in different sensory conditions (Hedrich et al. 2009, J Neurophys). Projection neurons are influenced by many extrinsic inputs (Rossignol et al. 2006, Physiol Review), but the responses of discrete classes of projection neurons vary: some are very similar to others while some show substantially different responses. Little is known about whether the anatomical organization of projection neurons contributes to these response profiles. We are using the crustacean stomatogastric nervous system to examine this issue, aiming to better understand the roles of projection neurons in motor pattern selection. Here, we are particularly interested in the topological and structural identification of projection neurons in the commissural ganglia (CoGs) of C. Borealis. Each CoG contains around 20 neurons projecting to downstream motor circuits (Coleman et al. 1992, J Comp Neurol). An

unknown number of projection neurons that innervate other targets plus local interneurons involved in sensory processing are also present. Relative somata location was determined using a combination of retrograde backfills of projection neuron axons and CoG cell membranes stainings with lipophilic fluorescent dyes (Goldsmith et al. 2014, PLoS ONE). A topological reconstruction of the commissural ganglia was achieved by analyzing stacks of 100 individual photos in different focal planes (2 μm steps) for each CoG. A non-rigid registration was applied to stacks from several CoGs to put them into a common coordinate system. We used landmarks like the particularly large L-cell (Cooke & Goldstone, 1970, J Exp Biol) to help align the photos. Overall CoG topology was fairly stable across ganglia. CoGs had an approximate oval shape with average major and minor axis of 537.65±59 and 400.72±44 μm, respectively, and average dorsal to ventral size of 171±12 μm (N=4). We observed an average of 139.25±30 (N=20) CoG somata with diameters ranging from 5 μm to 75 μm, of which 74±5.2% were smaller than 20 μm. Our initial analysis shows that at least for larger cells somata location was rather conserved across ganglia. Projection neurons innervating the same target circuits were distributed across several layers of CoG cells, with some clustered together dorsally near the entrance of their axons to the CoG. We are currently testing whether there is segregation of projection neuron somata to discrete CoG regions and whether this may contribute to their distinct responses to sensory activity.

Disclosures: R. Follmann: None. **C.J. Goldsmith:** None. **W. Stein:** None.

Poster

798. Rhythmic Motor Patterns: Afferent and Descending Control

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Topic: D.11. Vertebrate and Invertebrate Rhythmic Motor Pattern Generation

Support: Illinois State University RSP Cross-Disciplinary Grant Development Program

Title: Compartmental Hodgkin-Huxley model equations applied to the study of axonal modulation

Authors: *E. ROSA[1], R. FOLLMANN[2], W. STEIN[2];
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Abstract: Axons, although often thought of as mere conductors of action potentials, may have an important role in neuronal information and encoding. Ionotropic and metabotropic receptors for transmitters and neuromodulators found along the axon trunk can alter conduction velocity,

induce spike failures and initiate ectopic spiking, all of which in turn are capable of influencing information generation and processing. While these facts have long been ignored, recent advances in electrophysiological, imaging and molecular techniques show that the properties of the axon trunk potentially increase the computational capability of the neuron (Bucher et al, Prog Neurobiol 2011). Yet, these effects are difficult to study and an in-depth understanding of the influence of axon trunk modulation on the dynamics of spike propagation and initiation is still amiss. To provide insights into these dynamics, we are studying axon modulation in a Hodgkin-Huxley model of an axon trunk, consisting of a series of compartments with active properties. The model produces measurable action potential propagation delays, displaying a clear history-dependence and a concomitant change in firing rate at the distal end. Axon modulation causing ectopic spiking was implemented by altering the excitability of a few axonal compartments in the middle of the trunk. In specific, we added an h-current I_h to these compartments, since this current has been shown to be present and modulated in motor axons (Ballo et al, J Neurosci 2010) and we have experimental evidence that it underlies ectopic spiking in sensory axons (Daur et al, Frontier Comp Neurosci 2012). We found conceptually different effects on spike initiation and propagation: action potential velocity decreased with I_h and the relative timing of some action potentials at the distal end changed, indicating that changing axonal excitability is a mechanism for modulating *en passant* action potential propagation. Second, we found that ectopically generated action potentials in the middle of the axon affected action potential initiation at the proximal axonal segment with potential important consequences for neural coding. To initiate action potentials in the proximal segment, a ramp-shaped current injection was injected in compartment 1 to elicit bursts, mimicking slow synaptic input or peripheral sensory responses. Our preliminary data show that the structure of the elicited bursts depended on the ectopic spike frequency at the central spike initiation zone. Thus, not only action potential propagation but also encoding of sensory or synaptic information may be influenced by ectopic spiking.

Disclosures: **E. Rosa:** None. **R. Follmann:** None. **W. Stein:** None.

Poster

798. Rhythmic Motor Patterns: Afferent and Descending Control

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 798.04/P30

Topic: D.11. Vertebrate and Invertebrate Rhythmic Motor Pattern Generation

Support: NSF IOS-1153417

Title: Differential modulation of circuit feedback determines activity rate of a circuit input

Authors: *D. M. BLITZ;
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Abstract: Similar to many neural circuits, those underlying rhythmic behaviors (central pattern generators: CPGs) provide feedback to their projection neuron inputs. However, little is known regarding the function of such feedback. We are investigating roles of CPG feedback in the crab, *Cancer borealis,* stomatogastric nervous system. Extrinsic inputs (sensory, modulatory) activate projection neurons with different activity patterns and rates, which in turn enable projection neurons to elicit distinct chewing rhythm versions. During chewing, feedback neurons regulate projection neuron activity patterns, as occurs across rhythmic motor systems. Here I determine whether CPG feedback also regulates projection neuron activity rate. Brief stimulation of mechanosensory or peptidergic modulatory neurons each triggers long-lasting excitation of an identified projection neuron, CPN2, but each triggers different chewing rhythm versions (Blitz & Nusbaum, J Neurosci, 2008). I find that CPN2 firing rate was higher with CPG feedback intact than with feedback blocked, when CPN2 activity was triggered by the mechanosensory neurons ($p<0.001$, $n=10$) but not when triggered by the peptidergic neurons ($p>0.05$, $n=5$). Specifically, CPN2 activity rate was higher with CPG feedback only during the phase of the rhythm when the feedback neuron Int1 is silent. I thus determined CPN2 responses to pauses in Int1 activity. Brief pauses in Int1 activity triggered CPN2 rebound bursts after mechanosensory stimulation, but not under control conditions ($n=3$). To determine why the impact of this feedback synapse changed, I measured Int1 inhibitory synaptic currents (IPSCs) in CPN2. I found that mechanosensory stimulation triggered an increased Int1 IPSC amplitude ($p<0.01$, $n=4$). Increased Int1 activity alone was not sufficient to alter IPSC amplitude ($p=0.5$; $n=2$), suggesting modulation of the Int1 to CPN2 synapse. Thus, I propose that increased Int1 feedback strength elicits a higher activity rate because it triggers a rebound burst, which increases CPN2 rate above that due solely to direct mechanosensory effects. Conversely, I find that peptidergic neuron stimulation, after which feedback does not impact CPN2 activity rate, decreased Int1 IPSC amplitude ($p=0.02$, $n=2$). Thus, the modulatory status of CPG feedback determines not only the activity pattern (Blitz & Nusbaum, J Neurosci, 2012) but also the activity rate of a projection neuron input, thereby shaping motor circuit output. These results highlight the flexibility of circuit feedback and the importance of incorporating plasticity at this stage of a motor pathway into our understanding of how particular motor outputs are selected.

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Poster

798. Rhythmic Motor Patterns: Afferent and Descending Control

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Topic: D.11. Vertebrate and Invertebrate Rhythmic Motor Pattern Generation

Support: NIH Grant RO1 DC012859

NIH Grant R01 DC006876

Title: A circular model for song motor control in Serinus canaria

Authors: *G. B. MINDLIN[1], A. AMADOR[2], R. ALONSO[2], M. TREVISAN[2], F. GOLLER[3]; [1]universidad buenos aires, buenos aires, Argentina; [2]UBA, Buenos Aires, Argentina; [3]U. Utah, Salt Lake city, UT

Abstract: We built a model for birdsong production, whose variables are the average activities of different areas of the song system. One of the areas will be in control of the expiratory activity during song production, which is highly associated with different song features and can be compared to the actual behavior. We test the hypothesis that it is possible to construct a model in which 1. The activity of this area fits the observed expiratory patterns used by canaries, and 2. Another of the areas is sparsely active, simultaneously with significant motor instances of these patterns. We show that in order to achieve these two requirements, the area involved in the control of expiratory pulses needs to receive two inputs: a direct one, and its copy after processing by other areas of the song system. The model makes specific predictions on the timing of HVC activity for different classes of pressure patterns.

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Poster

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EICCI from the Cluster of Excellence 227 (CITEC), DFG

Title: Common mechanisms and specializations in force detection and control in cockroaches, stick insects and *Drosophila*

Authors: *S. N. ZILL[1], A. BüSCHGES[2], J. SCHMITZ[3], D. NEFF[4], S. CHAUDHRY[1]; [1]Anat. and Pathology, J.C. Edwards Sch. Med., Huntington, WV; [2]Dept. of Animal Physiology, Zoological Inst., Univ. of Cologne, Cologne, Germany; [3]Dept. of Biol. Cybernetics, Univ. of Bielefeld, Bielfeld, Germany; [4]Dept. of Chem., Marshall Unversity, Huntington, WV

Abstract: Detection of forces is an integral component of leg use in posture and locomotion. Information from receptors that monitor forces in multi-jointed legs may be particularly important in neural control of muscles as modular groups (synergists). We have performed comparative studies to characterize force detection and control in insects, using physiological studies in stick insects and cockroaches to gain insight into comparable mechanisms in fruit flies (*Drosophila*). Campaniform sensilla are mechanoreceptors that encode forces as cuticular strains through caps in the exoskeleton. The caps are organized in groups and the receptor responses are determined by the cap position and orientation. Previous studies have shown that the trochanteral and femoral groups are important in reinforcing muscle synergies. Current studies using confocal and light microscopy have identified many groups of sensilla that are homologous but the structure and responses of the femoral group (fCS) and mobility of the trochanter-femur joint (TrF) are species specific. Experiments to date indicate that in cockroaches, the TrF joint is mobile and movements are produced by a single muscle opposed by an elastic (resilin) band; the fCS are highly sensitive to posterior forces when the joint is engaged but relatively insensitive to forces in the almost perpendicular plane of movement of the coxo-trochanteral joint. In stick insects, the TrF joint is fused and fCS receptors discharge to both posterior forces and forces in the joint plane. The sensitivity to forces in the joint plane may be correlated with effects on muscle synergies: in stick insects, the fCS have strong effects on muscle synergies; in cockroaches, the dorsal campaniform sensilla (Gp3), that encode forces in the joint plane, have similar effects on use of leg muscles as synergists. Finally, in *Drosophila*, the fCS are the largest group of CS and are located on the ventral side of the femur in a position relative to the joint plane corresponding to the cockroach dorsal trochanteral sensilla. The position and orientation of the fCS in *Drosophila*, therefore, suggest that they should be sensitive to forces in the joint plane. Current experiments are characterizing the receptors in all serially homologous legs. Our working hypothesis is that receptors fulfill similar principal functions in different species but the effects of individual groups are determined by the specific forces they encode. These findings on force detection and muscle synergies may be paralleled in other animals, including vertebrates.

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Poster

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Topic: D.11. Vertebrate and Invertebrate Rhythmic Motor Pattern Generation

Title: Central coupling between locomotion and respiration in the metamorphosing frog

Authors: *D. COMBES, L. MERLET, M. THOBY-BRISSON, D. MORIN, J. SIMMERS; Univ. of Bordeaux, CNRS UMR 5287, BORDEAUX, France

Abstract: Xenopus metamorphosis involves a complete change of locomotor mode from tail-based undulatory swimming in tadpoles to adult quadrupedal locomotion. In parallel, the respiratory system switches from aquatic to aerial breathing. At critical stages, functional larval and adult locomotor and respiratory systems must co-exist in the same animal, implying a progressive reconfiguration of underlying neural circuitries and their functional interactions. The isolated brainstem produces, under high K+ saline, spontaneous respiratory output consisting of stage-specific patterns of bilaterally-synchronous impulse bursts in cranial motor nerves. In early premetamorphic tadpoles, high frequency, low intensity bursts corresponding to fictive gill ventilation are continuously generated by the caudal brainstem. Episodic waves during which the intensity of those bursts increases are observed in later premetamorphic stages. In postmetamorphic froglets, short and high intensity bursts are produced at lower frequency, corresponding to fictive lung breathing. Both rostral and caudal brainstem regions contribute to this adult motor pattern as evidenced by their persistent rhythmogenic capability after separation by a transverse section at the level of the VIIth nerve. Pulmonary bursting appears at prometamorphic stages and becomes increasingly present through the course of metamorphosis. The use of isolated brainstem-spinal cords with combined recordings of respiratory cranial nerves and spinal (in tadpoles) or limb (in froglets) motor roots also allowed us to explore the interaction between the two motor systems. In tadpoles where axial locomotion and gill breathing are used, each spontaneous locomotor episode is followed by a series of rhythmic respiratory bursts. Specific brainstem hemisections indicated that this coupling is mediated by ipsilateral ascending excitation of the brainstem respiratory networks from each side of the spinal cord. In postmetamorphic froglets that express appendicular locomotion and lung respiration, each spontaneous locomotor episode occurs conjointly with an episode of respiratory bursts triggered by an excitatory influence in time with limb extensor burst activity. Thus, in both pre- and post- metamorphic Xenopus, an efference copy of locomotor network activity provides a central coordinating drive to brainstem respiratory circuitry. We are now addressing how the underlying coupling pathways are adapted to changing locomotor strategy during

metamorphosis, especially at climax where the two modes of locomotion and respiration require complex dynamic interactions between all four co-existing networks.

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Poster

798. Rhythmic Motor Patterns: Afferent and Descending Control

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Title: Effects of mechanical perturbations on fictive locomotion in the lamprey

Authors: D. R. BERNALES[1], *E. D. TYTELL[2];
[1]Biol., Boston Univ., Boston, MA; [2]Dept. of Biol., Tufts Univ., Medford, MA

Abstract: The neuronal circuit that generates locomotion in vertebrates, called a central pattern generator (CPG), is found in the spinal cord. This circuit produces rhythmic signals to contract the muscles and bend the body for locomotion. It also receives and processes proprioceptive sensory inputs. During locomotion, however, all animals must cope with unexpected stimuli that may affect or disrupt the normal locomotor pattern. In this project, we aim to understand the effect of such perturbations on the lamprey CPG, and how the CPG corrects itself to compensate after being disrupted. We isolated the spinal cord of the silver lamprey Ichthyomyzon unicuspis and evoked fictive locomomotion using D-glutamate in the bath. To mimic the normal swimming motion, we bent the spinal cord from one side to another using a motorized arm. As previously observed, the bending motion could entrain the CPG's rhythm over a range of frequencies. Once the CPG was entrained, we added brief triangle-wave perturbations at a range of different phases to the baseline bending pattern. We varied both the amplitude and the frequency of the baseline bending frequency and examined how the response to perturbations varied. We then measured the timing of the first burst that came after the perturbation, and compared it to when it would have occurred if the perturbation had not happened, constructing a phase response curve. Across five individuals, the change in the burst phase after the

perturbation is linearly related to the phase of the perturbation itself, but the perturbation does not simply reset the burst phase. Instead, perturbations that occur before a burst tend to delay the next burst and those that occur after a burst tend to advance the next one. We also compared the effect of the perturbations on their own, with no baseline bending, to their effect when superimposed on a sinusoidal bending motion. By themselves, the perturbations produce a much smaller effect than when they are superimposed on the bending motion, and the shape of the phase response curve is quite different. These results will help us to characterize how the lamprey and other vertebrates respond adaptively to perturbations during normal locomotor behavior.

Disclosures: D.R. Bernales: None. **E.D. Tytell:** None.

Poster

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Support: VR Grant 11554

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Title: Reticulospinal neurons transmitting commands for modification of spinal reflex responses to body bending during escape behaviors in lampreys

Authors: L.-J. HSU, P. V. ZELENIN, *G. N. ORLOVSKY, T. G. DELIAGINA;
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Abstract: In the lamprey, the proprioceptive information is provided by stretch receptor neurons (also known as edge cells, EC). They are located at the margins of the spinal cord and activated by longitudinal stretch of this area during body bending. ECs, when activated by lateral bending, cause activation of motoneurons on the convex side during fast forward swimming, and on the concave side during escape behaviors (slow forward swimming, SFS; backward swimming, BS; lateral turns, LT). These spinal reflexes, mediated by ECs, can be reversed by supraspinal signals. In the lamprey, supraspinal commands are transmitted mainly by reticulospinal pathway. The aims of the present study were: (i) to reveal reticulospinal neurons (RSNs) transmitting supraspinal commands for modification of EC-mediated reflexes in context of escape behaviors,

and (ii) to clarify if RSNs receive sensory feedback from ECs. For this purpose, the *in vitro* preparation consisting of the brainstem and spinal cord was used. To monitor EC-mediated reflexes evoked by lateral bending of the spinal cord, activity in ventral roots was recorded. Stimulation of specific sites of n. trigeminus was used to cause reversal of EC-mediated reflexes, as well as to evoke different types of escape behaviors. To reveal RSNs causing reflex reversal, RSNs were recorded intracellularly during EC-mediated reflexes, before and during stimulation that caused the reversal. Two groups of RSNs, differently activated by stimulation of the ipsi- and contralateral n. trigeminus, were found, suggesting that they transmit commands for the reflex reversal. Group 1 neurons were activated by stimulation of any n. trigeminus, and Group 2 neurons - by stimulation of the contralateral nerve only. Group 1 neurons and the majority of Group 2 neurons were located in the middle rhombencephalic reticular nucleus. We found that Group 1 neurons were activated during SFS and BS, suggesting that they caused reversal of EC-mediated reflexes during these behaviors. In contrast, during LT the reversal of reflexes was caused by neurons of both groups. To reveal sensory inputs from ECs to RSNs, responses of individual RSNs to bending of the spinal cord were recorded. We found that 76% of RSNs (located in different reticular nuclei) responded to bending, suggesting that they receive sensory feedback from ECs. Thus, in the present study two groups of RSNs transmitting commands causing reversal of EC-mediated reflexes during escape behaviors have been found, and existence of the sensory feedback from ECs to RSNs has been demonstrated.

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Poster

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Title: The neural basis for regional body bending in zebrafish startle behavior

Authors: *H. R. KATZ[1], Y.-C. LIU[3], M. E. HALE[2];
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Abstract: A major question on the organization of the vertebrate nervous system is how regionalization evolved in the spinal cord. In larval zebrafish, axial bending has generally been categorized as either anterior to posterior travelling waves that occur during rhythmic swimming or large unilateral bends of startles and maneuvers. We have recently described a third pattern of bending that occurs during a subtype of startle behavior, the formation of an axial standing wave with a rostral bend to one side of the body and caudal bend to the other. This movement pattern is more similar to tetrapod locomotion than other axial bending patterns previously described in larval zebrafish. By examining the mechanistic basis of this movement pattern, we aim to gain insights into potential mechanisms for regionalized bending in the zebrafish spinal cord. First, we performed behavioral kinematic studies in larval zebrafish to better characterize the two bends observed in the standing wave. This behavior can only be elicited by a caudal stimulus, so we used a tactile stimulus at different locations along the caudal region of the body. We found that the two bends are always produced in the same position along the body axis and do not vary with stimulus location, supporting the idea that there is a discrete demarcation between rostral and caudal regions. Second, we investigated the mechanism for the localization of these bends. Previous work has found no evidence of discrete organization of motor neurons or interneurons in these regions of the body axis. Our data on reticulospinal neurons indicate that they also do not play a role in this localized activity. We have identified Rohon Beard (RB) cells, a type of somatosensory cell, as a major sensory input that produces this regional, localized bending. Paired recordings have shown that caudal RBs synapse directly onto commissural local cells which inhibit contralateral caudal motor neurons and ultimately signal an S-start. This finding led us to investigate sensory input as a potential mechanism for regionalized motor activity. Because we only observe this inhibition in the caudal region, it suggests that there is regionalization in RB subtype distribution. Using both *in vivo* confocal imaging of GFP-labeled somatosensory neurons and antibody staining, we explore rostro-caudal differences in RB arborization and dendritic projections in zebrafish larvae to better understand how these subtypes may be distributed. This work may shed light on an early form of discrete regionalization within the vertebrate spinal cord and inform our understanding of how more pronounced regionalization may have evolved.

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Poster

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Title: Activity of individual spinal neurons during locomotion initiated from brainstem and from spinal cord

Authors: *P. V. ZELENIN[1], P. E. MUSIENKO[2], O. V. GORSKII[2], V. F. LYALKA[1], Y. P. GERASIMENKO[2], G. N. ORLOVSKY[1], T. G. DELIAGINA[1];
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Abstract: In quadrupeds, the basic neural mechanisms controlling locomotor limb movements are located in the spinal cord. At present, operation of these mechanisms is poorly understood. Spinal locomotor networks can be activated by signals from the brainstem, as well as by direct stimulation of the spinal cord. The aim of the present study was to characterize the activity of the same individual spinal neurons under these two conditions, i.e., when locomotion is evoked by stimulation of the mesencephalic locomotor region (MLR), and when it is evoked by stimulation of the spinal cord (SC). For this purpose, these two modes of stimulation were used in the decerebrate cat to induce the hindlimbs walking on the treadmill. Spinal neurons were recorded in L4-L6 by a multi-electrode array (32 recording sites). Activity of individual neurons was extracted from the mass activity by spike-sorting procedure. We found that activity of most neurons was modulated in the locomotor rhythm, with a burst of activity in a definite part of the step cycle, and much lower activity between the bursts. Though SC-evoked locomotion is more dependent on peripheral feedback than MLR-evoked locomotion, we found that the phases of modulation of individual neurons were similar during locomotion initiated from these two sites, suggesting that the same spinal locomotor networks were activated in both cases. We divided all step-related neurons into five groups (S1-S5) according to the burst position in the step cycle, variability of this position, and burst shape. We suggested that the neurons responsible for generation of a step cycle have less variable activity than their targets outside the generator, and selected neurons with a smaller dispersion of their activity phase. Two distinct groups of such neurons were found. The S1 neurons generated a short-lasting burst in the swing phase of the step cycle or close to this phase. The S2 neurons generated a long-lasting burst in the stance phase, with a gradually increasing (ramp-shaped) firing rate. We suggest that these two groups

(each containing about 10% of all neurons) determine the swing and stance phases of the step cycle, respectively. To explain sequential generation of these phases, we propose an asymmetrical model of the step generator, in which SR2 neurons cause excitation of S1 neurons, whereas the latter cause inhibition of S2 neurons. Neurons of other groups (S3-S5) have a larger variability of the burst position in the cycle and of the burst pattern. We suggest that these neurons integrate inputs from S1 and S2 neurons and are responsible for activation of motoneurons of different limb muscles during step.

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Poster

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Title: Pre- and post-synaptic inhibitory mechanisms acting on lumber spinal cord neurons during generalized motor inhibition induced by stimulating the medullary reticular formation in the decerebrate cat

Authors: *K. TAKAKUSAKI;
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Abstract: An activation of the reticulospinal tract arising from the medullary nucleus reticularis gigantocellularis (NRGc) induced muscular atonia (generalized motor inhibition) in acutely decerebrated cat. We have demonstrated that this tract induced postsynaptic inhibition upon forelimb and hindlimb motoneurons and lumbar interneurons in reflex pathways. The inhibitory effects were possibly mediated by lamina VII interneurons that received inhibition from volleys in flexion reflex afferents (FRA) (Takakusaki et al. 2001, 2003; Habaguchi et al., 2002). The present study was designed to elucidate whether the reticulospinal tract also mediated presynaptic inhibition in primary afferents. For this purpose, we employed 14 decerebrate cat preparations. After identification of the medullary inhibitory region by stimulating the medial part of the NRGc (50Hz and 30-40 μA), the cats paralyzed and artificially respired. Then

potentials in dorsal root filaments of L6 segment and those in the ventral root filaments of L7-S1 segments were monitored. Short train pulses of stimuli (3 pulses, 5 ms interval and 30-40 μA) applied to the inhibitory region in the NRGc evoked negative potentials in the ventral roots and positive potentials in the dorsal root. The former had onset latency of 20-30 ms and peak latency of 50-60 ms, and the latter had onset latency of 10-20 ms and peak latency of 50-60 ms. Intracellular recordings of lumbar motoneurons (n=67) showed that the NRGc stimulation invariably evoked inhibitory postsynaptic potentials (IPSPs) whose time course was mostly the same as those in the negative ventral root potentials. Moreover, intra-axonal recordings revealed that the identical stimuli induced primary afferent depolarization (PAD), an indicator of presynaptic inhibition, in 50 % of intra-axonal sensory afferents (Ia fibers; n= 6/12, Ib fibers; n= 5/11 and cutaneous afferents; n= 7/13). The time course of the PAD was nearly the same as that of positive potentials in dorsal roots. These potentials were reduced in size when stimulating electrode was moved from the optimal site to dorsal, ventral and lateral sites. Moreover these potentials were reduced in size when conditioning volleys in FRA was preceded to the NRGc stimulation. These findings suggest that the reticulospinal tract from the medullary NRGc contribute to muscular atonia by both presynaptic and postsynaptic inhibitory mechanisms, which may be mediated by inhibitory interneurons in lamina VII of Rexed.

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Poster

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PIFI-PROMEP-VIEP

Catedra Moshinski

Title: Phase resetting of the respiratory rhythm elicited by the activation of a distinct central pattern generator

Authors: *R. MEZA-ANDRADE[1], B. DE LA TORRE-VALDOVINOS[1], N. HUIDOBRO[1], P. LINARES[1], R. TECUANHUEY[2], E. MANJARREZ[1];

[1]Inst. de Fisiología, [2]Facultad de Medicina, Benemérita Univ. Autónoma De Puebla, Puebla, Mexico

Abstract: Phase resetting is a behavior in which the cycle period of a rhythm changes by a particular perturbation. Several studies have demonstrated a respiratory phase resetting which can be produced by stimulation of various nerves and structures related to the upper airways, as well as cortical and midbrain structures. However, to our knowledge there are no studies about a respiratory phase resetting produced during the activation of another rhythm generator unrelated to the respiratory centers. The aim of the present study was to show experimental evidence of a respiratory phase resetting elicited by the activation of the spinal central pattern generator (CPG) of scratching. This is relevant because the phase resetting elicited by physiological stimuli may shed light on the organization of a CPG and its interaction with other structures. Experiments were performed in five acute precollicular-postmammillary decerebrate cats. Extracellular unitary recordings of ipsilateral respiratory neurons from the ventrolateral and dorsal medulla were obtained by means of quartz-platinum/tungsten microelectrodes from Thomas Recording (1 to 3 MΩ). Additionally, electroneurograms of the ipislateral phrenic nerve (C5) as well as of the tibialis anterior and medial gastrocnemius nerves were simultaneously recorded. In all the experiments we found a significant respiratory phase resetting during episodes of fictive scratching in neurons of the hypoglossal nerve nucleus (n=2), the phrenic nerve (n=5), as well as inspiratory (n=9) and expiratory (n=3) neurons of the ventral respiratory column. We observed that the inspiratory neurons were activated during fictive scratching, whereas the expiratory neurons were silenced. The motor outputs were differentially affected: the phrenic nerve exhibited altered firing activity, while the hypoglossal nucleus was silenced. These results show the first evidence of a phase resetting produced by neuronal elements related to one CPG on another CPG. Specifically, we demonstrated the phase resetting of the respiratory rhythm elicited by the activation of a non-overlapping and functionally distinct central pattern generator.

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Poster

799. Rhythmic Motor Patterns: Models

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Title: Bistability facilitates multifunctionality and improves performance in a neuromechanical model of motor pattern generation

Authors: *D. LYTTLE[1], J. GILL[2], K. SHAW[2], P. THOMAS[3], H. CHIEL[2];
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Abstract: Motor systems in many animals are multifunctional, meaning that a single neuromechanical system is able to produce multiple, qualitatively different rhythmic motor behaviors (e.g. walking vs. running). We explore the consequences of the coexistence of multiple stable dynamical regimes in a biomechanically coupled model central pattern generator circuit, with sensory feedback governing the transitions between regimes. As a concrete example, we focus on a nominal neuromechanical model of the feeding apparatus of the marine mollusk *Aplysia californica*. In this model, three mutually inhibitory neural pools drive a biomechanical model of the *Aplysia* buccal mass, while proprioceptive feedback from the feeding apparatus is in turn sent back to the nervous system. At each cycle, the feeding apparatus attempts to grasp seaweed (represented as a fixed resisting force), but only succeeds in doing so with some probability. Once a piece of seaweed has been successfully grasped, the system must consume the entire seaweed strip before attempting to grasp another one. We find that the model can operate within two distinct regimes, and that the system exhibits bistability between the two. In the "heteroclinic regime", the system is sensitive to proprioceptive feedback from the muscles, which selectively prolongs specific motor phases. In the "limit cycle regime", the timing of the pattern is insensitive to proprioceptive feedback, and the oscillations are faster. These two regimes also differ in their responses to brief neural and mechanical perturbations. We find that the limit cycle dynamics are superior for grasping seaweed, whereas the heteroclinic dynamics are superior for consuming seaweed once it has been grasped. Moreover, we find that overall feeding performance is improved when the system can flexibly transition between regimes. Thus, neuromechanical bistability may allow motor systems to produce robust and flexible behaviors in a variable environment.

Disclosures: **D. Lyttle:** None. **J. Gill:** None. **K. Shaw:** None. **P. Thomas:** None. **H. Chiel:** None.

Poster

799. Rhythmic Motor Patterns: Models

Location: Hall A

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Topic: D.11. Vertebrate and Invertebrate Rhythmic Motor Pattern Generation

Support: NIH grant NS047073

NSF grant DMS-1010434

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Title: Preparing the periphery for a subsequent behavior: Motor neuronal activity during biting generates little force but prepares a retractor muscle to generate larger forces during swallowing in *Aplysia*

Authors: *H. LU, J. M. MCMANUS, M. J. CULLINS, H. J. CHIEL;
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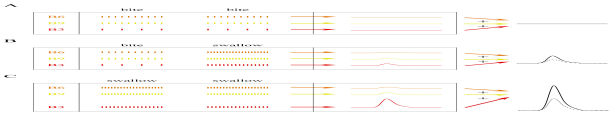
Abstract: Some behaviors occur in obligatory sequence, such as reaching prior to grasping an object. Can the earlier behavior serve to prepare the musculature for the later behavior? If it does, what is the underlying neural mechanism of the preparation? To address this question, we examined two feeding behaviors in the marine mollusk *Aplysia* californica, one of which must precede the second: biting and swallowing. Biting is an attempt to grasp food that does not succeed; once an animal does grasp food, it immediately switches to swallowing to ingest food. The main muscle responsible for pulling food into the buccal cavity during swallowing is the I3 muscle, whose motor neurons, B6, B9 and B3 have been previously identified. By performing recordings from these neurons *in vivo* in intact, behaving animals or *in vitro* in a suspended buccal mass preparation, we demonstrated that the frequencies and durations of these motor neurons increased from biting to swallowing. Using the physiological patterns of activation to drive these neurons intracellularly, we further demonstrated that activating them using biting-like frequencies and durations, either alone or in combination, generated little or no force in the I3 muscle (illustrated by part A in the figure). When biting-like patterns preceded swallowing-like patterns, however, the forces during the subsequent swallowing-like patterns were significantly enhanced (illustrated by part B in the figure). Sequences of swallowing-like patterns, either with these neurons alone or in combination, further enhanced forces in the I3 muscle (illustrated by part C in the figure). These results suggest a novel mechanism for enhancing force production in a muscle, and may be relevant to understanding motor control in vertebrates.



Disclosures: **H. Lu:** None. **J.M. McManus:** None. **M.J. Cullins:** None. **H.J. Chiel:** None.

Poster

799. Rhythmic Motor Patterns: Models

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Support: NSF IIS-1065489

NSF DMS-1010434

NIH 1R56NS087249-01A1

Title: A kinematic model of surface conformational changes in the *Aplysia* feeding grasper

Authors: *C. E. KEHL[1], D. NEUSTADTER[2], S. LU[1], H. CHIEL[1];
[1]Biol., Case Western Reserve Univ., Cleveland, OH; [2]Calore Med. LTD, Or Akiva, Israel

Abstract: Biomechanics, the study of how the mechanics of the body affects both its capabilities and constraints, is the complementary partner to neural control for creating behaviors. The biomechanical properties of soft bodied organisms are a particularly challenging area for study, and have clinical implications for understanding such structures as tongues and the digestive system. These organisms can also serve as the basis for soft bodied robots, which can manipulate and maneuver through environments to which rigid systems might not have access. We have previously presented a kinematic model of the feeding grasper of the sea slug, *Aplysia californica*, derived from the segmentation of high resolution static magnetic resonance images (MRI). We have extended this model to incorporate segmentation of structures within the grasper from lower resolution MRI movies. The surface of the grasper overlies a complex musculature that allows it to open and close and to move towards the jaws (protraction) or towards the esophagus (retraction). Within the complex musculature are muscles known as the I4 and I6 muscles which form a horseshoe shaped structure through which an extension of the surface, known as the radular stalk, can move up and down. At the anterior of the I4/I6 muscles is a structure known as the prow, which may aid the grasper to protract through the jaws. The revised model suggests that rotation of the stalk and its movement towards and away from the prow plays a role in changes to the shape of the grasping surface. In addition, *in vivo* lesion studies and work with reduced preparations has led us to focus on the role of fine muscle fibers that attach underneath the grasping surface (sub-radular fibers). These fibers seem to be responsible for some of the changes in shape that the surface undergoes during opening and closing. Iteratively incorporating these features into our model allows it to conform more closely to the actual biological system, and provides insight into the detailed neural control of this flexible grasper.

Disclosures: **C.E. Kehl:** None. **D. Neustadter:** None. **S. Lu:** None. **H. Chiel:** None.

Poster

799. Rhythmic Motor Patterns: Models

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Topic: D.11. Vertebrate and Invertebrate Rhythmic Motor Pattern Generation

Support: NSF IIS-1065489

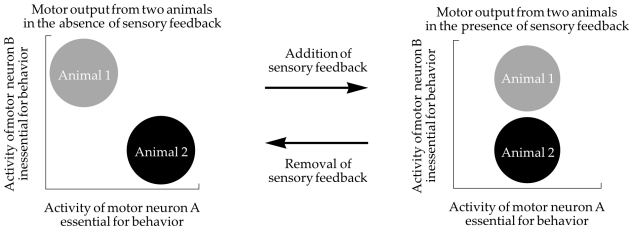
NSF DMS-1010434

Title: Getting to the right solution: Sensory feedback reduces motor neuronal individuality to satisfy behavior-specific biomechanical constraints

Authors: *J. P. GILL[1], M. J. CULLINS[1], J. M. MCMANUS[1], H. LU[1], K. M. SHAW[1], H. J. CHIEL[2];
[1]Dept. of Biol., [2]Depts. of Biol., Neurosci., and Biomed. Engin., Case Western Reserve Univ., Cleveland, OH

Abstract: Animals must continuously solve motor control problems posed by a variable environment. However, nervous systems are often intrinsically variable, and individuals also vary. How is this variability regulated so highly individual animals achieve comparable behavioral success? We hypothesized that intrinsic variability among individuals is constrained in motor neurons whose activities are essential for behavioral success, and sensory feedback is the mechanism that regulates this variability (see figure). To investigate this hypothesis, we studied rhythmic pattern generation in an animal model in which the majority of motor neurons controlling multiple behaviors are identified and can be simultaneously recorded during normal behavior. We quantified identified motor neuron activity mediating biting and swallowing in intact, behaving *Aplysia* californica. We measured multiple motor components: duration of activity of identified motor neurons and their relative timing during ingestive motor patterns. At the same time, we measured behavioral success: amplitude of grasping movement during biting, and amplitude of food movement during swallowing. By correlating motor neuronal activity with behavioral success, we obtained measures of motor neuronal efficacy. Biting and swallowing are distinct behaviors in which motor neurons may play different roles, so we expected to find differences in motor neuronal efficacy between biting and swallowing. Motor neuronal activity that was essential for the expression of biting or of swallowing was similar among animals, whereas motor neuronal activity that was not essential for that behavior varied more from individual to individual. What is the role of sensory feedback? We found that the removal of sensory feedback in the isolated ganglia increased individuality in the activity of motor

components most correlated with behavioral success. These results demonstrate that at the level of identified motor neurons, sensory feedback reduces motor neuronal variability when that activity matters for behavior.



Disclosures: **J.P. Gill:** None. **M.J. Cullins:** None. **J.M. McManus:** None. **H. Lu:** None. **K.M. Shaw:** None. **H.J. Chiel:** None.

Poster

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Topic: D.11. Vertebrate and Invertebrate Rhythmic Motor Pattern Generation

Support: NSF-DMS 1412877

Title: Modeling the Caenorhabditis elegans locomotion network: an opportunity in connectivity

Authors: ***G. HASPEL**[1], C. O. DIEKMAN[2];
[1]Biol. Sci., [2]Mathematical Sci., New Jersey Inst. of Technol., Newark, NJ

Abstract: The neuronal connectivity dataset of the nematode Caenorhabditis elegans has attracted wide attention from computational neuroscientists and experimentalists because it is currently the only organism-level connectome. However, the original electron micrographic dataset is incomplete, leaving 21 of 75 motoneurons of the locomotor network with partial or no connectivity data. Modeling efforts to date have either ignored the gap in data or used a simplified network that includes about half of the neuronal classes and omits most synaptic connections. We recently described how the existing connectivity dataset can be extrapolated into a complete neuromuscular network by identifying rules of connectivity (Haspel and O'Donovan 2011, J Neurosci 31(41):14611-14623). Here we use an extrapolated network that spans the full length of an animal and includes all the motoneurons of different classes, all muscle cells, and all synaptic connections, both chemical and electrical. The output of the network is the activity pattern of the muscle cells that can be directly interpreted as body

curvature. This level of comprehensiveness provides a unique opportunity to investigate network function within the constraints of its structure. We used an evolutionary algorithm to estimate cellular and synaptic parameters by optimizing over parameter sets to produce a propagating, dorsoventral alternating muscular activity that resembles the natural output of the locomotion network. We then assessed the importance of specific neuronal connections and [combinations of connections] by iteratively omitting random sets of connections from a pattern-producing network. We suggest that this novel virtual ablation approach to evaluating the importance of neuronal connections is useful when complete anatomical connectivity datasets (connectomes) of other animals become available. Together, these studies point out possible modes for the network to produce its output, within the constraints of known neurons, muscle cells, and their connectivity. All components of the model are identifiable in the real network and the results lead to experimentally testable predictions.

Disclosures: G. Haspel: None. **C.O. Diekman:** None.

Poster

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Topic: D.11. Vertebrate and Invertebrate Rhythmic Motor Pattern Generation

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Title: Mechanisms of sensory feedback governing motor network dynamics in a locomotor circuit

Authors: *B. CHUNG[1], R. CLEWLEY[2], D. EDWARDS[2];
[2]Neurosci. Inst., [1]Georgia State Univ., Atlanta, GA

Abstract: Here, we use a perspective from dynamical systems to ask how the output of a locomotor network is organized across postural and actively rhythmic states. We show that while sensory feedback to the network based on its motor output changes the burst period, it does not qualitatively reorganize the dynamic structure of the network. Also, a subset of interneurons is necessary to organize three qualitatively different activity regimes. A computational model of the locomotor network controlling the first joint of each walking leg in crayfish was developed based on known elements of the circuitry [1]. Simulation results showed that the network model

accounted for reflexes and patterns of bursting activity observed from *in vitro* experiments [1, 2]. By varying the amount of tonic excitation driving the circuit model, we found that there are three distinct regimes of network activity: quiescence, bursting, and tonic spiking. In closed loop simulations, when sensory feedback to the network was based on its motor output, as well as in open loop simulations, when there was no sensory feedback, there were no differences in the boundaries of the activity regimes. In the quiescent regime, only resistance reflexes that act against imposed perturbations were present. In the bursting regime, the period of closed loop bursts was shorter than that of bursts in open loop simulations and both resistance reflexes and assistance reflexes that act to amplify imposed perturbations were present. Finally, when tonic excitation was increased further, the network entered a tonically active state in which one pool of motor neurons fired continuously interrupted only by short bursts of the antagonist motor pool. In order to identify the mechanisms that organize network activity in this way, we tested the effect of changing specific elements. Hyperpolarization of assistance reflex interneurons eliminated the tonic spiking regime and resulted in only quiescence and an extended bursting regime. These results suggest that sensory feedback in closed loop simulations reduces the network bursting period without affecting the organization of network dynamics. In addition, we showed that assistance reflex interneurons are necessary for the tonic firing regime of the network. By utilizing a network model of the locomotor circuit controlling the first joint of a walking leg in crayfish, we were able to identify and understand the organizing principles of the network's motor output. [1] Bacque-Cazenave, Julien, et al. Journal of neurophysiology (2014). DOI: 10.1152/jn.00870.2014. [2] Chung, Bryce, et al. Journal of neurophysiology (2014). DOI: 10.1152/jn.00248.2014.

Disclosures: **B. Chung:** None. **R. Clewley:** None. **D. Edwards:** None.

Poster

799. Rhythmic Motor Patterns: Models

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Topic: D.11. Vertebrate and Invertebrate Rhythmic Motor Pattern Generation

Support: Stipend to NH by DFG funded cluster of excellence 277, CITEC

Title: A CPG driven dynamic model for the study of active tactile sensing in an insect

Authors: ***N. HARISCHANDRA**[1,2], T. HOINVILLE[1,2], A. F. KRAUSE[2], V. DÜRR[1,2];
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Abstract: A prime aspect of autonomous behaviors in animals is the active exploration of their environment using different sensing systems, allowing them to achieve context-dependent control of actions. Active touch is one such sensory system. Here, we are introducing a general framework of coupled Central Pattern Generators (CPGs) to be used in the context of movement generation for active tactile exploration. CPGs are biological neural networks that produce rhythmic outputs without rhythmical inputs. Stick insects (Carausius morosus) show rhythmic tactile exploration behavior during walking with coordinated movement of two joints per antenna. The phase difference of the distal scape-pedicel (SP) joint and the proximal head-scape (HS) joint is ~20º with the SP joint leading. Moreover, ablating proprioceptive hair fields on the antenna has no effect on the overall pattern of inter-joint coordination but affects the working-ranges of both antennal joints. The neuronal network that generates rhythmic antennal movement is unknown, but it has been localized in the brain and shown to be sensitive to the muscarinic acetylcholine agonist pilocarpine. Here, we develop a 3D dynamic, skeletal model of the stick insect head and antennae with physically realistic parameters. It is driven by a CPG consisting of two layers: phase-coupled Hopf oscillators for rhythm generation and, pattern formation networks for capturing frequency characteristics of individual joint oscillations. The model captures the joint kinematics essential for generating quasi-rhythmic and coordinated antennal movements and successfully produces biologically realistic movements on the skeletal model. We found that the phase lead of the SP joint could vary from ~10º to ~30º without disrupting the characteristic, elliptical trajectory of the antennal tip. We suggest that the constant phase shift seen in the antennal joint movements is coded into the CPG. The model is able to simulate the effect of hair-field ablations on the joint kinematics by changing the amplitude and offset of the corresponding oscillator in the CPG network. We propose that these hair fields control the local effective stiffness of each joint by acting through a negative feedback loop. In summary, we propose that the rhythmic searching movement of the stick insect antennal system is more centrally controlled and the proprioceptors are acting locally to regulate the joint movements. Our 3D dynamic model is capable of mimicking neurophysiological phenomena and will be useful in experiments on adaptive tactile exploration systems both in computer simulations and on biomimetic robots.

Disclosures: **N. Harischandra:** None. **T. Hoinville:** None. **A.F. Krause:** None. **V. Dürr:** None.

Poster

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Topic: D.11. Vertebrate and Invertebrate Rhythmic Motor Pattern Generation

Support: NIH Grant NS048844

NIH Grant EB012855

NIH Grant HD032571

Title: Computer simulations of slope walking in the cat: Role of supraspinal input to extensor interneurons

Authors: *A. N. KLISHKO[1], S. N. MARKIN[2], N. A. SHEVTSOVA[2], M. A. LEMAY[3], I. A. RYBAK[2], B. I. PRILUTSKY[1];
[1]Sch. of Applied Physiology, Ctr. for Human Movement Studies, Georgia Inst. of Technol., Atlanta, GA; [2]Dept. of Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA; [3]Dept. of Bioengineering, Temple Univ., Philadelphia, PA

Abstract: During cat walking on horizontal level, hindlimb flexors and extensors are normally active in the opposite phases of the locomotor cycle, swing and stance, respectively (Smith et al., 1998; Markin et al., 2012). This suggests that these muscles are activated primarily by corresponding inputs from the CPG flexor and extensor half-centers (McCrea, Rybak 2008). Generally similar activity patterns occur during upslope walking, although the magnitude and duration of extensor bursts increase (Carlson-Kuhta et al. 1998; Gregor et al. 2006). However during downslope walking, the flexor-extensor alternation breaks down at the hip joint: all hip extensors become silent during the entire walking cycle, while hip flexor iliopsoas (IP) generates activity bursts in both swing and stance phases (Smith et al. 1998; Akyildiz et al. 2015). This activity pattern appears to contradict the bipartite organization of locomotor CPG and has been previously explained within the framework of the unit burst generators (Smith et al. 1998; Grillner, 1981). The goal of this study was to investigate whether patterns of muscle activity during slope walking could be reproduced using a neuromechanical model of cat hindlimbs controlled by a two-level bipartite CPG (Markin et al. 2015). Parameters of the CPG model were tuned to fit multiple data obtained during fictive locomotion in the cat, whereas parameters of the hindlimb musculoskeletal model were optimized to reproduce mechanics of level walking. We took into account that (1) the transitions between extensor and flexor phases usually occurred at peaks of IP fascicle and muscle-tendon unit length during level and slope walking, and (2) the activity of ankle and knee extensors before ground contact was not substantially different in downslope conditions vs. level walking, whereas the activity of hip extensors was considerably reduced (Akyildiz et al. 2015). Therefore we hypothesized that major change in the muscle activities during downslope walking is provided by additional supraspinal drive to spinal circuits at the CPG pattern formation level that control hip extensor motoneurons. This change in muscle activation could occur without significant changes in sensory feedback synaptic weights from muscle and cutaneous afferents. To test this hypothesis, the supraspinal drive to extensor interneurons at the CPG pattern formation level was optimized to obtain the best match between

simulated and recorded patterns of muscle activity at different slope conditions. We suggest that the major features of hindlimb activity during slope walking could be reproduced by a two-level bipartite CPG with changing supraspinal drive to the CPG circuits.

Disclosures: **A.N. Klishko:** None. **S.N. Markin:** None. **N.A. Shevtsova:** None. **M.A. Lemay:** None. **I.A. Rybak:** None. **B.I. Prilutsky:** None.

Poster

799. Rhythmic Motor Patterns: Models

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Program#/Poster#: 799.09/Q6

Topic: D.11. Vertebrate and Invertebrate Rhythmic Motor Pattern Generation

Support: NSF research Grant No. IIS-1065489

Title: A flexible dynamical architecture for neuromechanical modeling and robotic control

Authors: ***A. D. HORCHLER**[1], K. A. DALTORIO[1], A. KANDHARI[1], H. J. CHIEL[2,3,4], R. D. QUINN[1];
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Abstract: Stable heteroclinic channels (SHCs) are a dynamical architecture that, like biological pattern generators, can respond immediately to multi-sensory perturbations by modulating the dwell time at a particular phase of oscillation to vary force output, range of motion, or other characteristics of a physical system. SHCs are composed of sequences of saddle equilibrium points, which yields exquisite sensitivity. The strength of the vector fields in the neighborhood of these equilibria determines the responsiveness to perturbations and how long trajectories dwell in the vicinity of a saddle. For SHC cycles, the addition of stochastic noise results in oscillation with a regular mean period. We find SHCs are well-suited for modeling behaviors with smooth state transitions, e.g., using a set of muscles for a sequence of actions. SHCs can be responsive to noisy feedback, e.g., coordinating soft-body locomotion with many possible ground contacts. Further, for robotics applications, they are simple enough to run in real time on a microcontroller. To facilitate the use of SHC cycles as oscillators, we have derived analytic approximations for the mean and variance of the passage time through the neighborhood of a linear saddle equilibrium point. Combining these approximations with a convenient parameterization, we show how the desired mean sub-periods of individual saddles of noise-driven Lotka-Volterra SHC cycles can be directly (and independently) specified within 2% for a

typical parameter set. Further, after measuring the resultant simulated sub-periods over sufficient numbers of cycles, the noise magnitude can be adjusted to control the mean period with accuracy close to that of the integration step size. SHCTools, a Matlab toolbox, has been developed that implements the relevant equations and algorithms to aid in analyzing and visualizing SHC dynamics. With these relationships and design tools, SHCs can be more easily employed in engineering and modeling applications. We demonstrate the use of SHCs to control independently-actuated segments of a soft worm-like robot. This task is challenging because many compliant degrees-of-freedom must be coordinated while simultaneously maintaining physical constraints for effective locomotion. Load feedback from the robot's motors and the noisy Lotka-Volterra dynamics of the SHC controller are used to trigger transitions between expansion and contraction of each segment. The performance of our SHC controller is compared with that of an augmented finite state machine controller.

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Poster

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NASA Training Grant NNX12AN24H

Title: Coordination and control of hind limb stepping in a rat model

Authors: A. HUNT[1], N. SZCZECINSKI[1], E. ANDRADA[2], M. FISCHER[2], *R. D. QUINN[1]; [1]Mechanical and Aerospace Engin., Case Western Reserve Univ., Cleveland, OH; [2]Inst. of Systematic Zoology and Evolutionary Biology, Friedrich Schiller Univ. of Jena, Jena, Germany

Abstract: We have developed a controller for hind limb stepping in a rat model based on research in biology and neuroethology. This research utilizes computational neuroscience models of neurons and synapses arranged in pathways discovered and theorized in the spinal cords of walking animals. These pathways are used to coordinate different joints together and control force output of the muscles. Desired muscle force activation patterns are calculated through inverse dynamics of high speed x-ray videos of walking rats. A four neuron central pattern

generator (CPG) model is analyzed and the results are used to develop a CPG which oscillates robustly while still responding to sensory feedback from the system. Critical network parameters are then trained to produce the desired motor neuron patterns through a combination of genetic and simplex search methods. This results in robust stepping patterns which reject perturbations and produces motions which are remarkably similar to that of a walking rat.

Disclosures: **A. Hunt:** None. **N. Szczecinski:** None. **E. Andrada:** None. **M. Fischer:** None. **R.D. Quinn:** None.

Poster

799. Rhythmic Motor Patterns: Models

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Program#/Poster#: 799.11/Q8

Topic: D.11. Vertebrate and Invertebrate Rhythmic Motor Pattern Generation

Support: NIH CoBRE P20GM109098

IDeA CTR – NIH/NIGMS U54GM104942

Title: Minimalistic central pattern generator for quadrupedal locomotion

Authors: *K. TUNTEVSKI[1], S. YAKOVENKO[2];
[1]Neurosci., West Virginia Univ. - Ctr. For Neurosci., Morgantown, WV; [2]Neurosci., WVU, Morgantown, WV

Abstract: Robust and computationally light models of the dynamic interactions that drive the spinal central pattern generator (CPG) of locomotion in mammals have been in demand for some time as they have a translational potential between quadrupedal animal models and human bipedal locomotion (McDermott, et al., 2011; Hoellinger et al., 2013). For this purpose, we have previously developed a leaky integrator model using ordinary differential equations (ODE) to describe the output of the spinal CPG for regular overground locomotion. The model consists of four leaky oscillators representing the temporal activity of motoneuron populations innervating flexor or extensor muscle groups on each side of the spinal cord, where contralateral flexor-extensor connections are mutually excitatory, while contralateral flexor-flexor and extensor-extensor interactions are inhibitory. The system is velocity driven and responds linearly to increasing input gain (Yakovenko, 2011), modeled as external parameters set from higher points on the motor control hierarchy (Prochazka & Yakovenko, 2007). The model parameters are iteratively optimized using error functions between recorded experimental and simulated outputs

accounting for the range of simulated velocities, the modulation of the stance phase duration as a function of step cycle duration (Halbertsma, 1983), and mismatch in coordination between bilateral phases and optimized using a Nelder-Mead heuristic downhill simplex method. Presently, we have expanded the model to accommodate asymmetric bipedal output, as well as quadrupedal forelimb-hindlimb synergistic interactions that are observed in healthy animal locomotion. The dynamic locomotor network was assayed with a precise foot placement locomotor task, which is known to require cortical activation for effective execution (Yakovenko et al., 2011). The task imposes spatial asymmetry to challenge either side of the motor cortex, and the temporal asymmetry between the left and right limb step cycles, termed the asymmetry index, and further shows promise for evaluation of both unimpaired and deficient locomotor networks.

Disclosures: K. Tuntevski: None. **S. Yakovenko:** None.

Poster

799. Rhythmic Motor Patterns: Models

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Program#/Poster#: 799.12/Q9

Topic: D.11. Vertebrate and Invertebrate Rhythmic Motor Pattern Generation

Support: NIH CoBRE P20GM109098

IDeA CTR – NIH/NIGMS Award Number U54GM104942

Title: Analytical solution to leaky integrator model of central pattern generator for locomotion

Authors: A. SOBINOV[1], *S. YAKOVENKO[2];
[1]Neurosci., West Virginia Univ., Morgantown, WV; [2]Human Performance, WVU Sch. of Med., Morgantown, WV

Abstract: Periodic movement is controlled by oscillatory activity produced by neural elements termed the Central Pattern Generators (CPGs). CPGs can be expressed using systems of simple coupled leaky integrators, which is a system of ordinary differential equations (ODEs). The input-output relationship of these models is usually obtained using numerical methods associated with computational errors and additional parametric analyses. In particular, the velocity hypothesis, stating that the desired forward velocity drives the CPG, was supported by inverse numerical calculations only (Yakovenko, 2011). However, for some models analytical solutions may exist. Here, we present piece-wise analytical solution to the system of ODEs that provide

the dynamics of state evolution between phase transitions. It has the form: $x = A^{-1}(exp\{At\} - I)B + exp\{At\}x_0$, where x & x_0 denote a state vector and its value at the starting time, respectively; t is time; A is a matrix of leak values for integrators and the weights for connections between them; B is the input to the system, and I is the identity matrix. The combination of this solution with the relationship between speed of movement and the cycle duration (Goslow et. al., 1973) shows the result that is consistent with the hypothesis that the speed is linearly dependent on the input to this system. Our finding supports the hierarchical organization of neural processing for the execution of locomotion. References: 1. Yakovenko S. A hierarchical perspective on rhythm generation for locomotor control. Prog Brain Res 188: 151–166, 2011. 2. Goslow GE, Reinking RM, Stuart DG. The cat step cycle: hind limb joint angles and muscle lengths during unrestrained locomotion. J Morphol 141: 1–41, 1973.

Disclosures: **A. Sobinov:** None. **S. Yakovenko:** None.

Poster

799. Rhythmic Motor Patterns: Models

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 799.13/Q10

Topic: D.11. Vertebrate and Invertebrate Rhythmic Motor Pattern Generation

Support: NSF CAREER Award DMS-1056125

Title: Sparsity and inhibition in the pre-Bötzinger complex can explain levels of synchrony and the presence of expiratory neurons

Authors: ***K. D. HARRIS**[1], T. DASHEVSKIY[3], E. T. SHEA-BROWN[2], J.-M. RAMIREZ[3]; [1]Univ. of Washington, Seattle, ; [2]Applied Mathematics, Univ. of Washington, Seattle, WA; [3]Ctr. for Integrative Brain Res., Seattle Children's Res. Inst., Seattle, WA

Abstract: The pre-Bötzinger complex (preBot) is now recognized as the essential core of respiratory rhythm generation and the inspiratory phase in particular. It is well known that the mechanism of rhythmogenesis is inherently excitatory, in contrast to canonical models of pattern generation such as the half-center, via an emergent network synchronization phenomenon. Using a biophysical model of the entire preBot, we examine how rhythmic activity of the population changes due to (1) the sparsity of connections between cells, (2) the fraction of cells which are inhibitory, and (3) the strength of excitatory and inhibitory synapses. We find that too much sparsity or inhibition disrupts rhythm generation, yet highly connected networks without inhibition also produce non-biological rhythms. As inhibitory neurons are added to the network,

some cells fire out-of-phase with the main population (inspiratory) rhythm, which offers an explanation for the expiratory cells observed in preBot. However, it is not possible to produce a two-phase (inspiratory-expiratory) population rhythm in our model without adding further structure to the network. These modeling results are compared to *in vitro* slice experiments in which we progressively block inhibitory and excitatory synaptic transmission. Slices exhibit rhythms that appear poised in the intermediate range of synchrony, and the fraction of expiratory cells *in vitro* is consistent with our model in this region. Being near the synchrony boundary may facilitate control of this rhythm. This offers a new paradigm for pattern generation where sparsely-coupled groups of cells act collectively as a single oscillator.

Disclosures: K.D. Harris: None. **T. Dashevskiy:** None. **E.T. Shea-Brown:** None. **J. Ramirez:** None.

Poster

799. Rhythmic Motor Patterns: Models

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Topic: D.11. Vertebrate and Invertebrate Rhythmic Motor Pattern Generation

Support: RO1 HL126523

Title: Homeostatic plasticity maintains stable respiratory rhythmic activity within the pre-Bötzinger Complex

Authors: *N. A. BAERTSCH[1], J. M. RAMIREZ[2];
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Abstract: Stable breathing is critical for survival. The network responsible for the generation of the respiratory rhythm is located within the medulla, and one particular area that is essential for breathing and specifically involved in the neuronal control of inspiration is the pre-Bötzinger Complex (PreBötC). Following isolation in transverse slices, the preBötC continues to generate stable inspiratory activity. The synchronized inspiratory population activity is transmitted to respiratory motor pools including the hypoglossal (XII) nucleus. Modeling and experimental studies suggest that synchronization and regularity of rhythmic activity is determined by the strength of excitatory conductances and the number of excitatory connections within this network. However, the mechanisms that establish the strength and number of excitatory interactions within this network are unknown. We hypothesized that mechanisms of activity-dependent homeostatic plasticity operate within the preBötC to regulate the stability of the

inspiratory rhythm. To test this hypothesis we isolated transverse brainstem slices containing the PreBötC from p5-10 CD1 mice. AMPA and kainite receptor-dependent synaptic activity was blocked overnight (16 hrs) in slices incubated with 10 μM DNQX in artificial cerebrospinal fluid (ACSF) containing 8 mM K^+ and continuously bubbled with carbogen; and compared to controls incubated for an equivalent duration in ACSF. Following $\geq$ 2 hrs of drug washout, rhythmic population activity was recorded from the PreBötC and XII motor nucleus. PreBötC burst amplitude irregularity score was reduced in slices exposed to DNQX (0.13±0.02), compared to controls (0.28±0.04). Also, transmission of PBC activity to the XII nucleus was improved following incubation in DNQX (100%) vs. controls (84%). Our data suggest that reduced excitatory synaptic activity revealed mechanisms of homeostatic plasticity that may operate within the PreBötC to maintain stable respiratory rhythm generation and reliable transmission to respiratory motor pools. Ongoing studies are using these manipulations to further explore the characteristics and molecular determinants that govern the stability of respiratory rhythmic activity.

Disclosures: N.A. Baertsch: None. **J.M. Ramirez:** None.

Poster

800. Striatal Dopamine Neurotransmission

Location: Hall A

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Topic: D.15. Basal Ganglia

Support: NIH Grant MH102930

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Title: Age-dependent effects of EEDQ on the affinity and efficacy of dopamine receptors in the caudate-putamen

Authors: A. MOHD-YUSOF, S. E. EATON, J. M. VALENTINE, D. E. HUMPHREY, A. E. GONZALEZ, C. A. CRAWFORD, *S. A. MCDOUGALL;
Dept. of Psychology, California State Univ., San Bernardino, CA

Abstract: Dopamine (DA) receptor inactivation differentially affects the expression of behavior across ontogeny. When administered systemically, *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) blocks the DA agonist-induced behaviors of adult rats, while leaving

the NPA- and quinpirole-induced locomotor activity of preweanling rats unaffected. This paradoxical behavioral effect is even more pronounced when drugs are microinjected into the caudate-putamen (CPu), because EEDQ-treated preweanling rats exhibit a potentiated locomotor response after NPA or quinpirole infusions. The neural basis for EEDQ's age-dependent behavioral effects is uncertain, but we propose that in younger animals a disproportionate number of surviving or newly repopulated D2 receptors exist in a high affinity state. Stimulation of these $D2^{High}$ receptors is hypothesized to cause the potentiated locomotor response exhibited by young rats. The purpose of the present study was to determine whether EEDQ treatment results in a relatively greater proportion of $D2^{High}$ receptors in preweanling rats when compared to adolescents and adults. We also examined the efficacy of D2 receptors by measuring agonist-stimulated [^{35}S]GTPγS binding in vehicle- and EEDQ-treated preweanling, adolescent, and adult rats. In both experiments, male rats were given an IP injection of vehicle or EEDQ (2.5 or 7.5 mg/kg) on PD 17, PD 39, or PD 84. After 24 h, CPu sections were bilaterally dissected and stored at -70 °C. For the $D2^{High}$ assays, duplicate incubation tubes contained 0.15 ml of homogenate, 1.2 nM [^{3}H]-domperidone, and various concentrations of DA. Nonspecific binding was determined in the presence of 10 μM (-)-sulpiride. Agonist-effect curves of [^{35}S]GTPγS binding were performed in assay buffer containing 10 μM GDP, 50–75 μg protein, and various concentrations of NPA. Nonspecific binding was determined in the presence of 10 μM cold GTPγS. Results showed that pretreating rats with EEDQ significantly increased the percentage of $D2^{High}$ receptors in the CPu. Importantly, the proportion of $D2^{High}$ receptors was elevated in preweanling rats relative to the other age groups. EEDQ also increased the efficacy (E_{max}), but not the potency (pEC_{50}), of NPA-stimulated [^{35}S]GTPγS specific binding. This increase in efficacy was significantly greater in preweanling rats than adults. Our findings are consistent with the hypothesis that a relative excess of high affinity, high efficacy D2 receptors produces a state in which DA agonists cause an exaggerated locomotor response in preweanling rats.

Disclosures: **A. Mohd-Yusof:** None. **S.E. Eaton:** None. **J.M. Valentine:** None. **D.E. Humphrey:** None. **A.E. Gonzalez:** None. **C.A. Crawford:** None. **S.A. McDougall:** None.

Poster

800. Striatal Dopamine Neurotransmission

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Topic: D.15. Basal Ganglia

Support: NRF-2010-0020408

NRF-2014R1A2A1A11052042

Title: Environmental enrichment enhances synaptic plasticity by internalization of striatal dopamine transporters

Authors: ***J. YU**[1,2], M.-S. KIM[1], J. SEO[1,2], M.-Y. LEE[1], S. WI[1,2], S.-R. CHO[1,2];
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Abstract: Environmental enrichment (EE) with a complex combination of physical, cognitive, and social stimulations enhances synaptic plasticity and behavioral function. However, the underlying mechanism remains to be elucidated in detail. In this study, we aimed to investigate dopamine-related synaptic plasticity underlying functional improvement after EE. For this, 6-week-old CD-1 (ICR) mice were randomly allocated to EE conditions or standard conditions for 2 months. EE significantly enhanced behavioral functions such as the rotarod test and the ladder walking test. We then investigated the expression pattern of dopamine transporter (DAT) using positron emission tomography (PET), and expression of DAT in the striatum significantly decreased by approximately 18% in the EE mice relative to the control mice. DAT inhibitor administrated to establish the relationship of the DAT down-regulation to the treatment effect also improved rotarod performance, suggesting that DAT inhibition recapitulated EE-mediated treatment benefits. Next, EE-induced internalization of DAT was confirmed using a surface biotinylation assay. *In situ* proximity ligation assay and immunoprecipitation demonstrated that EE significantly increased the phosphorylation of DAT in the striatum as well as the levels of DAT bound with protein kinase C (PKC). In conclusion, we suggest that EE enables phosphorylation of striatal DAT via a PKC-mediated pathway and causes DAT internalization. As a result of DAT internalization and dopamine reuptake inhibition in the presynaptic region, increased levels of dopamine in the neural synapse might lead to functional improvement. This is the first report to suggest an EE-mediated mechanism of synaptic plasticity by internalization of striatal DAT.This study was supported by the Ministry of Science, ICT & Future Planning (NRF-2010-0020408 and NRF-2014R1A2A1A11052042).

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Poster

800. Striatal Dopamine Neurotransmission

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Support: Parkinson's UK Studentship H-1003

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Title: Striatal dopamine transmission is weighted differently within the striosome-matrix axis by Substance P

Authors: K. R. BRIMBLECOMBE, *S. J. CRAGG;
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Abstract: The mammalian striatum has a topographical organization of input-output connectivity, but a complex intrinsic non-laminar neuronal architecture comprising projection neurons of two types interspersed among multiple interneuron types and potential local neuromodulators. From this cellular melange arises a compartmentalisation of areas termed striosomes and extra-striosomal matrix. The functions of these compartments are poorly understood but might confer distinct features to striatal signal processing and be discretely governed. Dopamine transmission occurs throughout striosomes and matrix, and is reported to be modulated by the striosomally enriched neuromodulator substance P. However, reported effects are conflicting, ranging from facilitation to inhibition. We addressed whether dopamine transmission is modulated differently in striosome-matrix compartments by substance P. We paired detection of evoked dopamine release at carbon-fiber microelectrodes in mouse striatal slices with subsequent identification of the location of recording sites with respect to μ-opioid receptor-rich striosomes. Substance P had bidirectional effects on dopamine release that varied between recording sites and were prevented by inhibition of neurokinin-1 receptors (NK1R). The direction of modulation was determined by location within the striosomal-matrix axis: Dopamine release was boosted in striosome centres, diminished in striosomal-matrix border regions and unaffected in the matrix. In turn, this different weighting of dopamine transmission by substance P modified the apparent centre-surround contrast of striosomal dopamine signals. These data reveal that dopamine transmission can be differentially modulated within the striosomal-matrix axis, and furthermore, indicate a functionally distinct zone at the striosome-matrix interface which may have key impact on striatal integration.

Disclosures: K.R. Brimblecombe: None. **S.J. Cragg:** None.

Poster

800. Striatal Dopamine Neurotransmission

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Topic: D.15. Basal Ganglia

Support: NIH Grant MH102930

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Title: Dopamine receptor inactivation in the caudate-putamen and nucleus accumbens differentially affects the locomotor activity of young rats

Authors: *K. RUDBERG, A. MORAN, J. RAZO, E. MACEDO, S. E. EATON, A. MOHD-YUSOF, C. A. CRAWFORD, S. A. MCDOUGALL;
Dept. of Psychology, California State Univ., San Bernardino, CA

Abstract: Microinjecting the alkylating agent EEDQ into the caudate-putamen (CPu) of adult rats both inactivates DA receptors and blocks DA mediated behaviors. In contrast, DA receptor inactivation in the CPu of preweanling rats causes a paradoxical increase in DA agonist-induced locomotor activity. We have hypothesized that the heightened behavioral responsiveness exhibited by EEDQ-treated preweanling rats is due to elevated levels of high affinity D2 receptors. In other words, an EEDQ-induced increase in the percentage of $D2^{High}$ receptors is proposed to more than compensate for the overall loss of DA receptors, thus resulting in enhanced behavioral responsiveness when challenged with a DA agonist drug (cocaine or NPA). The purpose of the present study was threefold: (1) to replicate the finding that EEDQ potentiates the behavioral effects of NPA when microinjected into the CPu; (2) to determine whether administering EEDQ into the nucleus accumbens (NAcc) also potentiates the effects of NPA; and (3) to examine whether the ability to potentiate or attenuate DA agonist-induced locomotion is influenced by the amount of striatal and accumbal tissue affected by EEDQ. On PD 17, different volumes (0.25, 0.5, or 0.75 µl) of EEDQ (100 µg) or DMSO were bilaterally infused into the NAcc or CPu. On PD 18, basal locomotor activity was assessed for 40 min, after which rats received bilateral infusions of vehicle or NPA (10 µg). Locomotor activity was measured for an additional 40 min. Autoradiographic analysis showed that EEDQ caused a volume-dependent reduction in D2 receptor binding in the CPu and NAcc (i.e., increased dispersion of EEDQ resulted in greater receptor loss) with, presumably, a concomitant increase in the percentage of $D2^{High}$ receptors. Consistent with this finding, microinjecting 0.75 µl EEDQ into the CPu potentiated the NPA-induced locomotor activity of preweanling rats, while lesser volumes of EEDQ left the behavior of rats unaffected. We believe that an EEDQ-induced increase in the percentage of CPu $D2^{High}$ receptors is responsible for the potentiated locomotor response. A similar potentiated behavioral effect was not observed when 0.75 µl EEDQ was microinjected into the NAcc. The most parsimonious explanation is that EEDQ-induced alterations in the percentage of NAcc $D2^{High}$ receptors was insufficient to support a potentiated

locomotor response in preweanling rats. Even so, administering EEDQ into the NAcc of preweanling rats did not block NPA-induced behavior, as normally occurs in adult rats. Thus, inactivating DA receptors in either the CPu or NAcc does not cause adult-like behavior patterns in preweanling rats.

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Poster

800. Striatal Dopamine Neurotransmission

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Topic: D.15. Basal Ganglia

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Division of Intramural Clinical & Biological Research of NIAAA

Title: Dorsal striatal mu opioid receptors inhibit cholinergic interneuron-driven dopamine release

Authors: *B. K. ATWOOD[1], Y. MATEO[2], D. M. LOVINGER[2];
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Abstract: Dopaminergic input to the dorsal striatum from the substantia nigra is important for many forms of striatal plasticity and striatum-mediated behaviors. The regulation of dopamine release in this brain region is complex and involves multiple neurotransmitters. The role of the mu opioid receptor (MOR) in regulating dopamine release from these inputs is unclear. Some studies show that MOR activation within the dorsal striatum decreases dopamine release, which is curious considering the absence of MOR on dopaminergic inputs. However, MORs found on cholinergic interneurons (CINs) may allow for regulation of dopamine release independent of direct effects on dopaminergic terminals. CINs make up less than 5% of striatal neurons, yet have extensively arborized axons that broadly influence neurotransmission. Acetylcholine released by these interneurons drives local striatal dopamine release by activating nAChRs on dopaminergic terminals. Recent evidence demonstrates that activation of MORs on CINs inhibits the activity of these neurons. We tested the hypothesis that MOR-mediated reduction of CIN activity is responsible for the effect of MOR agonists on dopaminergic transmission. We utilized fast-scan cyclic voltammetry to determine the effects of opioid ligands on dopamine release in

striatal brain slices. The MOR agonist DAMGO inhibited dopamine release elicited by both electrical stimulation and optogenetic activation of CINs. These data demonstrate that MORs are important regulators of CIN-driven dopamine release. We are currently exploring the effects of genetic manipulations of MOR expression on CIN-driven dopamine release.

Disclosures: B.K. Atwood: None. **Y. Mateo:** None. **D.M. Lovinger:** None.

Poster

800. Striatal Dopamine Neurotransmission

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Support: FRSQ postdoctoral fellowship

CIHR postdoctoral fellowship

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NARSAD

Title: Conditional knockout of tyrosine hydroxylase in midbrain dopamine neurons

Authors: *J.-F. POULIN, R. AWATRAMANI;
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Abstract: Dopamine (DA) is principally produced by neurons located in the midbrain and influences a spectrum of behaviors including motor, learning, reward, motivation, and cognition. In accordance with its diverse functions, DA dysfunction is implicated in a range of disorders affecting millions of people, including Parkinson's disease (PD), schizophrenia, addiction, and depression. To investigate DA function, we generated a mouse with a tyrosine hydroxylase (Th) conditional allele and used a Dat::iCre driver to embryonically delete Th, thus depriving midbrain neurons of their ability to synthesize dopamine. In contrast to previously published studies where a similar Cre line was used to deplete dopamine or ablate dopamine neurons in the midbrain, our cKO mice had a severe hypokinesia, weight loss, and did not survive past three weeks of age. These results suggest that embryonic DA depletion does not inevitably lead to compensatory mechanisms preserving motor function. This mouse model will be very helpful to study the role of DA in the developmental organization of striatal connectivity. In addition, the Th cKO mice will facilitate the investigation of the midbrain DA system by allowing to inhibit

the synthesis of DA in the newly identified DA neuron subtypes using specific genetic entry points.

Disclosures: J. Poulin: None. **R. Awatramani:** None.

Poster

800. Striatal Dopamine Neurotransmission

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1RO1NS073854

Simons Foundation Autism Research Initiative (SFARI)

Title: DHHC15-mediated palmitoylation modulates striatal dopamine levels and spontaneous locomotion

Authors: *R. M. MEJIAS-ESTEVEZ[1], A. ADAMCZYK[2], M. NIWA[1], I. N. KRASNOVA[3], G. M. THOMAS[4], M. HAN[1], J. WANG[5], Z.-X. XI[3], R. L. HUGANIR[1], M. PLETNIKOV[1], J. L. CADET[3], A. SAWA[1], T. WANG[1];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Drexel Univ., Philadelphia, PA; [3]NIDA, Baltimore, MD; [4]Temple Univ., Philadelphia, PA; [5]Univ. of Pennsylvania, Philadelphia, PA

Abstract: Dopamine (DA) is a major neurotransmitter in striatum and plays an important role in the modulation of activity, movement, rewards, motivation, and executive function. Regulation of striatal DA metabolism and signaling are extremely complex. Palmitoylation, a reversible lipid post-translational modification, is a newly recognized mechanism in the regulation of DA function. Several DA signaling proteins including dopamine transporter (DAT) and DA receptors (D1/D2L) are palmitoylated but their specific palmitoyl-acyl-transferases (PATs) have not been full characterized. Dat-knockout mice show extreme hyperactivity, reduced tissue DA levels and increased extracellular DA levels in striatum. We investigated a line of knockout mice of dhhc15, a neural-enriched PAT. Mutant mice exhibit an increase in the novelty-induced ambulatory activity in open field. Neurochemistry studies of monoamine levels in olfactory bulb, brain cortex, striatum, ventral mesencephalon, and hippocampal tissues in dhhc15-KO mice identified a significant and specific reduction of tissue dopamine and its metabolite, DOPAC in striatum. Interestingly, basal extracellular DA levels in ventral striatum of dhhc15-KO mice are

increased during the habituation time to a new environment using *in vivo* microdialysis methods. This profile suggests a partial DA reuptake or dopamine release defect in striatal dopaminergic neurons. Using an acyl-biotin exchange (ABE) assay, we found no significant difference in the steady-state palmitoylation levels of known DHHC15 substrates including postsynaptic density protein 95 (PSD95), growth associated protein 43 (GAP43), cysteine string protein (CSP), sortilin, and stathmin 2/3, in striatal tissues of dhhc15-KO mice. Characterization of palmitoylation levels of proteins involved in DA metabolism and signaling, including DAT and DA receptors, in the striatum of dhhc15-KO mice are in progress. Data from our studies implicate an important role of dhhc15-mediated pamitoylation in the regulation and release of striatal DA in mice.

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Poster

800. Striatal Dopamine Neurotransmission

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Title: Motor skill learning in rats is accompanied by phase-dependent modifications in the cAMP/PKA/DARPP-32 signaling pathway

Authors: *Y. QIAN[1], H. FORSSBERG[2], R. DIAZ HEIJTZ[1];
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Abstract: Abundant evidence points to a key role of dopamine (DA) in motor skill learning. However, the cellular and molecular pathways mediating its effects are still poorly understood. In this study, we used a skilled-reaching paradigm to identify brain activity patterns associated with different phases of motor skill learning. We studied the induction of the plasticity-related gene Arc (also known as Arg3.1), and investigated learning-induced changes in the DA system (from gene expression to biochemical modifications of intracellular pathways). In the early phase of motor skill learning, Arc mRNA was significantly induced in the cortico-striatal circuit, including the medial prefrontal cortex (mPFC), cingulate cortex, primary motor cortex, and striatum. In the late phase, however, a shift in the expression pattern of Arc was evident. Expression of Arc decreased significantly in most brain regions examined, except in the mPFC and dorsal striatum. There were also significant changes in the expression of DA D1 receptors and their intracellular target DARPP-32 in the striatum (but not cortical regions) during the early, but not late, phase of motor skill learning. Western blot analysis of the phosphorylation state of DARPP-32 and its downstream target CREB in the striatum indicated increased levels of phospho-Thr34-DARPP-32 (but not at the Thr75 or Ser97 sites) and phospho-Ser133-CREB during the early, but not late, phase of motor skill learning. These findings implicate the cAMP/PKA/DARPP-32 signaling pathway in the acquisition of novel motor skills, and also demonstrate a dynamic shift in the contribution of cortico-striatal circuitry during different phases of motor skill learning.

Disclosures: Y. Qian: None. **H. Forssberg:** None. **R. Diaz Heijtz:** None.

Poster

800. Striatal Dopamine Neurotransmission

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Topic: D.15. Basal Ganglia

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Title: Cortical and striatal induced motor tics in rats, behavioral and electrochemical studies

Authors: *J. CHANG, D. J. WOODWARD;
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Abstract: Tourette's syndrome (TS) is considered to be a neuropsychological disorder caused by basal ganglia thalamocortical system malfunction. Local injection of GABA antagonist in the striatum of different species yields an animal model of motor tics similar to that exhibited in patients with TS. Cortical regions, however, have been overlooked as a source of tic generation except few early studies in rats. It has been suggested that dopamine (DA) plays an important role in the pathophysiology of TS. However, detailed information about DA action during tics is elusive. Here we test the effect of microinjection of picrotoxin into the primary and secondary (M2) motor cortices to induce motor tics and compare with striatal injection. We also applied newly developed 8 channel fast scan cyclic voltammetry (FSCV) in conjunction with local microinjection technique to investigate the DA release in the striatum during motor tic. Microinjection of picrotoxin at a conventional dose of 1μg/1μl readily induced motor tics, but in some cases, especially in the M2 area, short lasting clonic seizures occurred. A low dose of picrotoxin (0.25-0.5μl/μl) injected into the motor cortices induced a motor tic similar to those initiated by striatal injection without behavioral and electrophysiological signs of seizures. No significant different in tic latency (measured between injection and first tic) was found between cortical and striatal groups while intervals between tics were significantly shorter in the cortical groups than the striatal group. FSCV detected periodic release at 40 s intervals of putative DA signals in regions surrounding the picrotoxin injection site in dorsal striatum. The phasic tics (at 3 s interval) thus were found superimposed on slow DA oscillations .The DA oscillations, not synchronized with individual tic, may be related to previously reported slow oscillation of firing rate in animal model and reaction time task in human patients as possible substrate of neuropsychological disorders. Single unit recording at the striatum injection site preceded activity in the substantial nigra reticulata as indicated by cross correlation analysis. This well controlled study demonstrated that an impaired GABA system both in the motor cortex or striatum mediates a local circuit pathology to generate motor tics. Our concept is that precision observation of modulation of tic generation will provide tools to assess ameliorative intervention.

Disclosures: J. Chang: None. **D.J. Woodward:** None.

Poster

800. Striatal Dopamine Neurotransmission

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Topic: D.15. Basal Ganglia

Support: NSF BRAIN EAGER DBI-1450767

Title: Modulation of basal dopamine in the nucleus accumbens following repeated low-dose ketamine exposure as measured using fast-scan controlled-adsorption voltammetry

Authors: M. A. MILLER[1], K. L. PARENT[2], M. A. BARTLETT[3], C. W. ATCHERLEY[2], D. F. HILL[4], T. FALK[3], M. L. HEIEN[2], *S. L. COWEN[5];
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Abstract: Ketamine is a common anesthetic that, when administered at sub-anesthetic doses, may be effective for the treatment of chronic pain, treatment-resistant depression, and L-DOPA-induced dyskinesia. Although ketamine is an NMDA antagonist and influences opioid and cholinergic receptors, few studies have investigated ketamine's impact on the release of dopamine in the nucleus accumbens. Understanding the impact of ketamine on nucleus accumbens dopamine concentration is important given dopamine's potential involvement in the anti-depressive and analgesic effects of ketamine administration. We investigated this issue by administering sub-anesthetic doses of ketamine (20 mg/kg) to an awake and freely behaving rat. Following a one-hour baseline collection period, a total of five i.p. injections of ketamine, each separated by two hrs, were administered over a 10 hr period. Basal dopamine concentrations were measured every 30 s using the recent-developed technology of fast-scan controlled-adsorption voltammetry (FSCAV). This technique permits measurement of basal dopamine concentration at temporal and spatial resolutions superior to techniques such as microdialysis. Using this approach, we observed 1) that following each ketamine injection there was an initial decrease in basal dopamine concentration (-17 ± 3% from time of injection within 13.9 ± 0.9 min, n = 5 injections/experiment, 3 experiments, ± SEM) that recovered after ~20 min and 2) stable basal dopamine levels increased following the five injections (23 ± 9 % above baseline during the final 30 min of measurement, n = 3 experiments, ± SEM), suggesting that repeated ketamine injection produces a persistent elevation of basal dopamine. Increases in basal dopamine levels may contribute to the effectiveness of ketamine for the treatment of depression, pain states, and the anti-dyskinetic effects reported by our group.

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Poster

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Support: DA010900

Title: A causal link between dopamine release and cue-responsivity at D2 receptors

Authors: *C. A. OWESSON-WHITE[1], A. M. BELLE[1], N. R. HERR[1], J. L. PEELE[1], P. GOWRISHANKAR[1], R. M. CARELLI[2], R. WIGHTMAN[1];
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Abstract: Dopaminergic neurons projecting from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) are crucial components of the brain-reward circuitry that drives approach behaviors necessary to acquire reinforcers such as foods.1 In the NAc, dopaminergic projections synapse on medium spiny neurons (MSNs), GABAergic cells that also receive glutamatergic input from the cortex, thalamus, hippocampus, and basal lateral amygdala.2,3 Understanding neurotransmitter actions at these synapses is necessary to elucidate mechanisms that can become high-jacked by drugs of abuse.4 Here we monitor brain activity with a carbon-fiber based probe5 that measures three independent components. Through cyclic voltammograms it quantifies synaptic dopamine overflow,6 through recordings of single-unit activity it simultaneously reveals neuronal firing rates,7 and through coupled micropipettes that form a microdelivery system for controlled iontophoresis, it allows identification of adjacent receptor subtypes in behaving animals.8 Its high spatial resolution for adjacent neurons and synapses, coupled to its high temporal resolution (subsecond) reveals local sites and time-points where specific neurotransmitter-receptor interactions occur. Here we show that a single dopamine concentration transient, triggered by a learned cue during intracranial self-stimulation (ICSS), a goal directed behavior, exerts modulatory responses on MSNs. Critically the data provide a causal link between dopamine release and the modulation of MSNs involved in cue responses by dopaminergic D2 receptors during a learned behavior.

Disclosures: C.A. Owesson-White: None. **A.M. Belle:** None. **N.R. Herr:** None. **J.L. Peele:** None. **P. Gowrishankar:** None. **R.M. Carelli:** None. **R. Wightman:** None.

Poster

800. Striatal Dopamine Neurotransmission

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 800.12/R3

Topic: B.07. Synaptic Transmission

Title: Methylphenidate modulates dopaminergic and glutamatergic transmission from ventral tegmental area to nucleus accumbens Shell

Authors: *C. REYES-VAZQUEZ, A. M. VAZQUEZ-ALVAREZ, B. PRIETO-GOMEZ; Depto. De Fisiología, Mexico DF, Mexico

Abstract: Dopaminergic (DA) neurons in ventral tegmental area (VTA) project to the core and shell subregions of the Nucleus Accumbens (NAc) in which DA release is induced by natural stimuli as well as by drugs of abuse. Synaptic transmission between VTA and NAc is critically involved in reward-motivated behaviors and thought to be altered in addiction. Also, glutamate (GLUT) is packaged and released by a subset of mesolimbic DA neurons, eliciting Excitatiory Postsinaptic Currents (EPSCs) onto medium spiny neurons in NAc. There is no information about the modulation of GLUT release from DA midbrain terminals by Methylphenidate (MTP). Using electrical stimuilation to selectively activate midbrain DA fibers, we compared the properties and modulation of EPSCs measured using whole-cell recordings in mouse brain slices. Mice (8-10 weeks old) were anesthetized with isoflurane and killed by decapitation. Brains were quickly removed, mounted, and sliced. Slice preparation and whole cell patch clamp recordings were performed using standart techniques. For electrical stimulation, a glass pipette filled with ACSF was placed in the NAc Shell and a rectangular pulse (0.2 ms) was applied every 2 min. The amplitude of the current pulse (100-250 μA) was adjusted to use the minimal current needed to generate a maximal and stable responses. Electrically induced EPSCs were inhibited by DA receptor D2R agonist and showed a marked paired-pulse depression that required 2 min for full recovery. MTP depressed EPSCs amplitude by 50% but enhanced the overall DA transmission from midbrain DA neurons. AMPA and NMDA receptor-mediated EPSCs were equally inhibited by MTP, suggesting a presynaptic mechanism of action. These findings demonstrate that acute MTP inhibits DA and glutamate release from midbrain DA neurons via presynaptic D2R but has differential overall effects on their transmissions in the NAc. Suggesting that MTP, by blocking DA reuptake, facilitates the feedback inhibition of DA and glutamate release from these terminals.

Disclosures: C. Reyes-Vazquez: None. **A.M. Vazquez-Alvarez:** None. **B. Prieto-Gomez:** None.

Poster

801. Basal Ganglia: Dopamine Neuron Physiology

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 801.01/R4

Topic: D.15. Basal Ganglia

Support: Monument Trust Discovery Award from Parkinson's UK (J-0901)

MRC award (MC_UU_12020/5 to P.J.M)

Investigator Award from the Wellcome Trust (101821 to P.J.M.)

MRC award (MR/J004324/1 to S.J.C.)

Title: Cell-type selective encoding of spontaneous movement by dopaminergic neurons

Authors: *P. D. DODSON[1,2], J. K. DREYER[4], K. A. JENNINGS[3], R. WADE-MARTINS[3,2], S. J. CRAGG[3,2], J. P. BOLAM[1,2], P. J. MAGILL[1,2];
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Abstract: Loss of dopaminergic neurons in Parkinson's disease results in a compromised ability to initiate movement. However, while it is clear from the symptoms of Parkinson's that dopamine is critical for appropriate motor function, it is generally thought that the firing of dopaminergic neurons does not change during movement. Using *in vivo* recording and juxtacellular labelling of individual, identified midbrain dopaminergic neurons in head-fixed mice, we show that neurons encode the onset of spontaneous movement with a pause in their firing. Moreover, we found that this movement-related firing was cell-type specific, with dopaminergic neurons in the substantia nigra pars compacta (SNc) but not ventral tegmental area (VTA) significantly decreasing their firing rate at movement onset. To determine whether brief, movement-related firing of dopaminergic neurons could be 'read out' in target structures, we used fast-scan cyclic voltammetry and computational modelling. We show that movement-related firing results in significant changes in extracellular striatal dopamine concentration and receptor signaling in striatal spiny projection neurons (SPNs). To investigate whether movement-related firing patterns are altered in Parkinson's disease, we recorded from SNc neurons in a Parkinson's mouse model (SNCA-OVX mice); these mice express moderately elevated levels of human alpha-synuclein and develop age-dependent motor impairment and neurodegeneration. Consistent with our previous findings in anesthetized SNCA-OVX mice, we found that in awake mice at rest, the firing rates of surviving SNc neurons were significantly lower compared to those in littermate controls. Moreover, encoding of movement by SNc neurons and the resultant movement-related striatal dopamine signaling was lost in Parkinsonian mice. These findings demonstrate a role of substantia nigra dopaminergic neurons in encoding movement-onset and suggest that loss of appropriate signaling may contribute to motor impairment in Parkinson's.

Disclosures: P.D. Dodson: None. **J.K. Dreyer:** None. **K.A. Jennings:** None. **R. Wade-Martins:** None. **S.J. Cragg:** None. **J.P. Bolam:** None. **P.J. Magill:** None.

Poster

801. Basal Ganglia: Dopamine Neuron Physiology

Location: Hall A

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Program#/Poster#: 801.02/R5

Topic: D.15. Basal Ganglia

Support: NIH grant DA038208

VA grant BX002525

Medical Research Foundation of Oregon

Portland Veterans Affairs Parkinson's Disease Research, Education, and Clinical Center

Title: AMP kinase activation augments K-ATP current in rat midbrain dopamine neurons

Authors: *S. W. JOHNSON[1,2], Y. WU[2], A. C. MUNHALL[1], K.-Z. SHEN[2];
[1]Dept Neurol, Portland VA Med. Ctr., Portland, OR; [2]Neurol., Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: AMP-activated protein kinase (AMPK) is a master enzyme that regulates expression of ATP-sensitive K+ (K-ATP) channels in pancreatic beta-cells and cardiac myocytes. Midbrain dopamine neurons also express K-ATP channels, and they can exert strong influences on neuronal excitability. The present study used whole-cell patch-clamp recordings to investigate effects of AMPK on K-ATP channel function in substantia nigra compacta dopamine neurons in slices of rat midbrain. We first examined the actions of the AMPK activator A769662 on K-ATP currents evoked by 200 μM diazoxide. When added to the pipette solution, the AMPK activator A769662 (5 μM) was associated with a significant increase in currents evoked by bath application of diazoxide, that being 472% of control when measured 60 min after starting whole-cell recording. Current evoked by the K-ATP channel opener NN414 (10 μM) also increased significantly to 338 ± 21% of control 60 min after starting superfusion. Activation of AMPK by A769662 was confirmed by Western blot analysis, which showed that A769662 induced a concentration-dependent increase in Thr-172 phosphorylation of AMPK in slices of rat midbrain. But as an unexpected finding, we found that diazoxide currents also increased over time when pipettes did not contain A769662; although currents also increased significantly to 300% of control, this was significantly less than the increase observed when A769662 was present ($P < 0.01$, t-test). Moreover, superfusing the slice with the AMPK blocking agent dorsomorphin (30 μM) significantly reduced diazoxide current to 38 ± 7% of control, whether or not A769662 was present in pipette solutions. Control experiments showed that repeated applications of the

GABA-B agonist baclofen evoked outward currents that were not altered by the presence of either A769662 or dorsomorphin over 90 min of recording. Moreover, diazoxide currents did not increase over time in subthalamic nucleus neurons when pipettes contained A769662. We conclude that AMPK activation augments the function of K-ATP channels in midbrain dopamine neurons. Our findings that AMPK activation did not alter diazoxide currents in subthalamic neurons or GABA-B currents in dopamine neurons suggest that AMPK exerts actions that are specific for types of neuron and ion channel.

Disclosures: **S.W. Johnson:** None. **Y. Wu:** None. **A.C. Munhall:** None. **K. Shen:** None.

Poster

801. Basal Ganglia: Dopamine Neuron Physiology

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 801.03/R6

Topic: D.15. Basal Ganglia

Support: NIH NINDS program grant NS003135 to Z.M.K.

Title: T-type calcium channels control non-linear dendritic integration in vulnerable subpopulation of substantia nigra dopamine neurons

Authors: *R. C. EVANS, Z. M. KHALIQ;
NINDS, NIH, Bethesda, MD

Abstract: Dopamine neurons burst in response to rewarding stimuli and pause in response to reward omission. Recent *in vivo* studies suggest that these bursts and pauses interact with each other, with pauses facilitating rebound bursts. One possibility is that hyperpolarization during the pause modifies intrinsic conductances and alters dendritic integration, enabling bursts in response to incoming excitatory input or disinhibition. However, little is known about how hyperpolarization affects dendritic excitability and synaptic integration in substantia nigra pars compacta (SNc) neurons. Using two photon calcium imaging and whole cell recording, we found that hyperpolarization modulates intrinsic conductances, facilitating a strong depolarizing rebound in SNc dopamine neurons. When we drove a 20Hz triplet of action potentials from a range of membrane potentials (-50mV to -90mV), we saw a long lasting afterdepolarization (ADP), and a concomitant large dendritic calcium transient emerge with increasing hyperpolarization. For example, the calcium amplitude in response to the triplet driven from -80mV was four times larger than the calcium amplitude in response to the same triplet driven from -60mV (-60mV: mean dG/Gs=0.031 n=42; -80mV: mean dG/Gs=0.133 n=94; p<

0.000001). In addition, we found that at -80mV, the size of the ADP correlated well with the size of the calcium transient (r=0.75, n=114). Applying TTA-P2, we found that the ADP and corresponding calcium transients depend on T-type calcium channels. Additional experiments along with computational modeling suggested that the high input resistance and tightly coupled dendrites characteristic of SNc dopamine neurons facilitate the generation of the ADP. Specifically, increasing membrane conductance by activation of GIRK potassium channel with baclofen, a GABAb agonist, eliminated the ADP. To test the effect of hyperpolarization on synaptic integration, we stimulated excitatory inputs onto the SNc dopamine neurons at increasing frequencies. We found that hyperpolarization increased the sensitivity of SNc neurons to input frequency, shifting the dendritic integration pattern from a linear to a non-linear mode. Lastly, we performed post-hoc immunostaining on recorded cells. We found that the hyperpolarization induced ADP is prominent in the calbindin negative subpopulation of SNc neurons, but substantially smaller in the calbindin positive subpopulation. Because a large ADP corresponds to a large global calcium influx, this novel characteristic may represent an increased calcium load and thus contribute to the selective vulnerability of the calbindin negative neurons in Parkinson's Disease.

Disclosures: R.C. Evans: None. **Z.M. Khaliq:** None.

Poster

801. Basal Ganglia: Dopamine Neuron Physiology

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 801.04/R7

Topic: D.15. Basal Ganglia

Support: NINDS IRP NS003135

Title: Ionic mechanisms of the post-burst pause in dopamine neuron subpopulations

Authors: *R. A. TARFA[1,2], Z. KHALIQ[1];
[1]NIH/NINDS, Bethesda, MD; [2]Neurosci., Brown Univ., Providence, RI

Abstract: Dopamine neurons (DA) contribute to a range of behaviors such as reward, motivation, and movement, which raises the question of whether functional differences exist between dopamine neuron subpopulations. Here, we tested heterogeneity in the firing properties and underlying ionic conductances of retrogradely-labeled mesostriatal (MS) and mesoaccumbal (MA) dopamine neuron subpopulations located in the substantia nigra (SNc) and ventral tegmental area (VTA). During goal-directed behaviors, dopamine neurons fire bursts of spikes

quickly followed by pauses. Therefore, we examined the ionic mechanism underlying high-frequency firing and the subsequent pauses. First, we compared firing evoked from fixed membrane potentials (between -65 and -70 mV) and found that MA and MS neurons displayed similar maximal spike rates. However, comparing the amplitude of the after-hyperpolarization (AHP) immediately following high-frequency spiking, we found that AHPs were significantly larger in MS neurons compared to MA neurons. Furthermore, AHPs were completely blocked by apamin, a blocker of small-conductance calcium-activated (SK) potassium channels, suggesting a more dominant role of SK channels in shaping the post-burst pause in MS neurons. *In vivo* experiments comparing the burst-pause sequence in dopamine neuron subpopulations have observed relatively longer pauses following bursts in MA dopamine neurons. We next examined the latency to the first spike in response to current injections evoked from fixed potentials (-70 mV). We found significantly longer latencies in MA versus MS neurons. In a similar comparison between spontaneously active VTA and SNc neurons, we found that the delay to first spike (i.e. rebound delay) following a brief (500 ms) hyperpolarizing current injections was typically longer in VTA versus SNc neurons. Bath application of AmmTX3 in both VTA and SNc neurons dramatically reduced the length of the rebound delay, consistent with a prominent role of A-type potassium currents. Past work has shown that A-type potassium currents contribute to the latency of first spike and rebound delays in midbrain dopamine neurons. We found that A-type potassium currents decayed significantly more slowly in MA dopamine neurons (avg inactivation time-constant, at -40 mV: 98.4 ± 12.21 ms, n = 13) as compared to the MS neurons (avg time-constant, at -40mV: 36.8 ± 6.0 ms, n = 10). Altogether, our findings suggest post-burst pauses in dopamine neurons result from the interaction of SK, A-type and H-currents, with SK and H-currents playing a more dominant role in the SNc neurons while A-type currents are more important in shaping pauses in VTA neurons.

Disclosures: **R.A. Tarfa:** None. **Z. Khaliq:** None.

Poster

801. Basal Ganglia: Dopamine Neuron Physiology

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 801.05/R8

Topic: D.15. Basal Ganglia

Support: Intramural Grant NS003135

Title: Influence of timing on integration of excitatory synaptic input during tonic firing in substantia nigra dopamine neurons

Authors: *T. A. HAGE, Z. M. KHALIQ;
NINDS/NIH, Bethesda, MD

Abstract: Dopamine neurons of the substantia nigra pars compacta display ongoing firing of action potentials (APs) at low rates both *in vivo* and in acute slices. As a result, excitatory synaptic inputs must be integrated on an ever changing membrane, unlike the stable resting potentials of typically silent neurons. There are multiple mechanisms by which the ongoing activity of dopamine neurons could influence synaptic inputs. First, synaptic and voltage-sensitive ion channels (e.g. NMDA receptors and low-voltage activated Ca channels) are more likely to be strongly activated towards the later phase of the spike cycle where the membrane potential nears AP threshold. Second, APs during tonic firing of dopamine neurons reliably backpropagate throughout the dendrites and produce large AP-evoked conductances that decrease membrane resistance and may shunt synaptic potentials. Using whole-cell recording, 2-photon Ca imaging and glutamate uncaging in acute mouse brain slices, we tested the influence of the timing of synaptic input relative to the phase of tonic firing. We find that the amplitude of glutamate-evoked synaptic Ca influx is nearly twice as large in the late phase of tonic firing, near AP threshold (phase = 0.75-1, $\Delta G/GS = 20.2 \pm 2.1\%$) than in the early phase, shortly following an AP (phase = 0-0.25, $\Delta G/GS = 10.6 \pm 1.5\%$). The amplitude of synaptic Ca influx in response to glutamate uncaging during the middle phase of the firing cycle (0.26-0.74) was intermediate ($\Delta G/GS = 15.7 \pm 1.4\%$). We measured the effect of glutamate uncaging on the timing of the subsequent AP as a function of the phase of tonic firing. We observe a U-shaped relationship in which synaptic input shortly following an AP has little effect on the timing of the next AP - likely due to weak synaptic strength ($2 \pm 4\%$ decrease in ISI). Synapse activation in the late phase of tonic firing also has little effect on the timing of the subsequent AP ($1 \pm 3\%$ decrease in ISI) despite increased synaptic strength, as the membrane voltage is already near AP threshold. Synaptic activation during intermediate phases of tonic firing significantly decreased the ISI by $12 \pm 3\%$. Ongoing experiments are aimed at determining the contributions of specific ion channels to shaping excitatory synaptic inputs during different phases of tonic firing.

Disclosures: T.A. Hage: None. **Z.M. Khaliq:** None.

Poster

801. Basal Ganglia: Dopamine Neuron Physiology

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 801.06/R9

Topic: D.15. Basal Ganglia

Support: Aotearoa Foundation NZ

University of Auckland FRDF Grant

Title: Optogenetic stimulation of the Subthalamic nucleus modulates downstream dopaminergic neurons in the Substantia Nigra pars compacta via endocannabinoids

Authors: *P. S. FREESTONE, K. L. TODD, Y. SUN, J. LIPSKI;
Univ. of Auckland, Auckland, New Zealand

Abstract: Endocannabinoids (eCBs) are cannabis-like substances produced by the brain which regulate synaptic transmission in a retrograde fashion by inhibiting presynaptic neurotransmitter release. We have recently shown a novel mechanism regulating GABAergic transmission onto dopaminergic neurons in the Substantia Nigra pars compacta (SNc) mediated by eCBs. Production of eCBs was initiated by spillover of glutamate, yet the source of the glutamatergic input was not determined. The Subthalamic nucleus is a major glutamatergic nucleus of the basal ganglia circuitry and plays a crucial role in the indirect and hyperdirect pathways of this network. The present study investigated the effect of the STN on the activity of dopaminergic neurons in the SNc, with focus on the role of eCBs. CD-1 mice expressed either channelrhodopsin (ChR2) or halorhodopsin (HR) under the CaMKIIα promotor after injection of viral (AAV) constructs into the STN. Neuronal activity was monitored using whole-cell and single-unit electrophysiological recordings from horizontal midbrain slices (300 μm thick) containing the SNc, STN and SN pars reticulata (SNr) after 4 - 8 weeks expression. The STN was selectively illuminated using a digital mirror device and a variety of stimulation patterns (constant on, 5 - 100 Hz, or Theta-burst; 30 sec duration, 4 ms pulse). Light activation of the STN in slices obtained from ChR2-expressing mice evoked a biphasic increase in dopaminergic neuron firing. The initial increase was reduced by bath application of CNQX (10 μM), while the delayed response was unaffected. In HR-expressing STN, a biphasic inhibition of firing was observed. The response supports an underlying glutamate driven disinhibition mediated eCBs, requiring further characterization using specific pharmacological tools.

Disclosures: **P.S. Freestone:** None. **K.L. Todd:** None. **Y. Sun:** None. **J. Lipski:** None.

Poster

801. Basal Ganglia: Dopamine Neuron Physiology

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 801.07/R10

Topic: D.15. Basal Ganglia

Title: Role of co-released glutamate from dorsal raphe serotonin neurons in substantia nigra

Authors: *H. ZHANG[1], L. CHEN[2], Q. QIN[3], L. ZHI[3], C. B. DIVITOA,[4], S. CHOI[6], Y. WANG[2], R. P. SEAL[5];
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Abstract: The serotonergic system is involved in the regulation of mood, aggression, sleep, and numerous other behaviors. Accumulating evidence suggests that a subset of raphe serotonin neurons may release glutamate as a cotransmitter to communicate with target neurons, however, this ability is still controversial and its roles wait to be elucidated. Dopamine (DA) neurons in the substantia nigra (SN) pars compacta plays key roles in movement and dysregulation of DA transmission has been strongly implicated in movement disorders such as Parkinson's disease. The other component of SN, SN pars reticulata (SNr) is a key basal ganglia output nucleus critical for movement control. In addition to excitatory inputs from the cortex and subthalamic nucleus, SN neurons are prominently innervated by serotonin neurons in the dorsal raphe (DR), however, up to date; the exact role played by the serotonin system in the control of midbrain SN neurons is still unclear. Here we use an optogenetic approach to investigate whether glutamate is co-released in SN and how serotonin and the co-released glutamate modulate the midbrain SN microcircuit. We selectively activated the serotonergic axons by expressing the light-activated cation channel channelrhodopsin-2 (ChR2) in genetically defined serotonin neurons in the raphe of wild-type (WT) and vesicular glutamate transporter 3 (VGLUT3) KO mice by injecting a virus encoding a cre-dependend ChR2-mcherry fusion protein into the dorsal raphe nucleus of Sert-Cre mice (> 2 month old). We performed whole-cell patch-clamp recordings in SN 3-8 weeks after surgery. We found that excitatory post-synaptic potentials (EPSCs) could be evoked by photo-stimulation of serotonergic terminals in the SN in the WT mice whereas was absent in the VGLUT3 KO mice. Serotonin terminals co-releasing glutamate mainly targeted GABA neurons in the SN and increased their firings upon activation. These data suggest that serotonergic neurons in dorsal raphe are capable of release glutamate in SN and may provide a fast sub-cortical control of SN microcircuits.

Disclosures: **H. Zhang:** None. **L. Chen:** None. **Q. Qin:** None. **L. Zhi:** None. **C.B. Divitoa,:** None. **S. Choi:** None. **Y. Wang:** None. **R.P. Seal:** None.

Poster

801. Basal Ganglia: Dopamine Neuron Physiology

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 801.08/R11

Topic: D.15. Basal Ganglia

Title: Model of the interaction of the axonal and somatic spike generating mechanisms in nigral dopamine neurons

Authors: *C. C. CANAVIER;
Cell Biol. and Anat., Louisiana State Univ. Hlth. Sci. Ctr., New Orleans, LA

Abstract: The action potential in midbrain dopamine neurons has two separable components, an axon initial segment (AIS) component and a somato-dendritic (SD) component. The AIS component can be isolated using antidromically evoked spikes while holding the soma hyperpolarized. The maximum firing range in these neurons is limited by depolarization block caused by the failure of the SD component. In order to model the temporal separation of these two components, we started with an existing model of a dopaminergic pacemaker neuron (Kuznetsova et al. 2010) with a morphology (Vetter et a.l 2001) downloaded from www.neuromorph.org and implemented in the simulation package NEURON. We then added an axon hillock and axon initial segment connected to a primary dendrite at variable distances from the soma. The NaV and delayed rectified channel density were larger in the AIS than elsewhere, and in some simulations, the half activation and inactivation of the NaV current were shifted in a hyperpolarized direction in the AIS to lower the threshold. The model reproduces many features of the published experimental data, including a latency between the spike in the axon-bearing dendrite (ABD) and that in the soma, as well as the near simultaneous spikes throughout the soma and nonABD dendrites. The AIS component is much more prominent in the model for antidromic compared to orthodromic spikes, such as those that occur during pacemaking *in vitro*. For some parameter settings we observed action potential reflection, which involves a second spike in the ABD driven by the SD in the rest of the cell (Gentet and Williams 2007). We incorporated a second, slow component of NaV channel inactivation in order to better capture entry into depolarization block. The results are highly dependent on the passive properties of the model neuron as well as the geometry and other parameters of the axon. The model can be used to understand back propagation of spikes during simulated *in vivo* firing patterns.

Disclosures: C.C. Canavier: None.

Poster

801. Basal Ganglia: Dopamine Neuron Physiology

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 801.09/R12

Topic: D.15. Basal Ganglia

Support: NS079750

1F31NS089716-01

Title: Cerebellar modulation of substantia nigra

Authors: *S. G. KEE, K. KHODAKHAH;
Dominick P. Purpura Dept. of Neurosci., Albert Einstein Col. of Med., Bronx, NY

Abstract: The graceful, precise, and well-timed movements of the human body are coordinated by a complex system of interconnected brain regions. Two subcortical structures, the cerebellum and basal ganglia, are responsible for fine-tuning motor output. Dysfunction of these structures is associated with a number of neurodegenerative diseases and movement disorders, including Parkinson's disease (PD), Huntington's disease, dystonia, and ataxia. Both structures are known to form a number of closed-loop circuits with the cerebral cortex, which, until recently was believed to be the primary site of interaction between these two brain areas; however, reports of reciprocal disynaptic connections between basal ganglia and cerebellum have challenged this view. There is anatomical and functional evidence in the literature that supports a connection from the cerebellar nuclei to the dopamine neurons of the substantia nigra pars compacta, by which the cerebellum can alter dopamine levels in the striatum. Here, we test the hypothesis that the cerebellum can modulate the substantia nigra through a direct, monosynaptic connection. To test this hypothesis, Channelrhodopsin (ChR2) was expressed in cerebellar nuclei neurons and an optrode was used to record from single units in substantia nigra while simultaneously activating cerebellar fibers in substantia nigra. Immunohistochemistry confirmed that cerebellar fibers expressing ChR2 were present in the tyrosine hydroxylase-positive region of the substantia nigra, corresponding to the pars compacta, but limited in the nearby parvalbumin-positive region of the substantia nigra, corresponding to the pars reticulata. Preliminary electrophysiology data suggest that neurons in the substantia nigra are excited in response to optogenetic activation of cerebellar fibers in substantia nigra. Taken together, these data provide support for an additional pathway capable of relaying information directly between the cerebellum and basal ganglia.

Disclosures: S.G. Kee: None. **K. Khodakhah:** None.

Poster

801. Basal Ganglia: Dopamine Neuron Physiology

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 801.10/R13

Topic: D.15. Basal Ganglia

Title: A new role for midbrain dopaminergic neurons during temporal judgments

Authors: S. SOARES[1], B. V. ATALLAH[1], T. S. GOUVÊA[1], T. MONTEIRO[1], *J. J. PATON[2]; [1]Champalimaud Fundation, Champalimaud Ctr. for the Unknown, Lisboa, Portugal; [2]Fundacao Champalimaud PT507131827, Lisbon, Portugal

Abstract: Encoding the passage of time is critical to behavior and cognition. Although classically referenced as key structures for reward based decision making and motor behavior, the basal ganglia (BG) are critical for encoding time on the scale of seconds. Yet, little is known about how distinct components of BG circuit contribute to the encoding of time. Here we probe the role of a critical component of the BG, midbrain dopaminergic (DAergic) neurons. We measured and manipulated the activity of DAergic neurons in mice performing a temporal discrimination task. In this task, mice learned to judge the delay between two tones as shorter or longer than a 1.5s boundary, reporting their judgements by entering one of two nose ports in order to earn a reward. To characterise the response properties of midbrain DAergic neurons during this task, we expressed GCaMP6f specifically in these neurons and recorded bulk fluorescence signals in awake, behaving mice. We observed large phasic responses tied to various task events, such as delay onset, delay offset and reward delivery. Notably, the amplitude of the response to delay offset was larger when stimuli were judged as short than when they were judged as long, regardless of whether the subsequent choice was correct. This suggests that short temporal judgements are correlated with higher midbrain DAergic activity. To test whether this relationship is causal, we photo-activated these neurons using channelrhodopsin-2 during task performance. This manipulation resulted in a horizontal shift in the psychometric curve towards shorter choices. Our results are consistent with the interpretation that activating midbrain DAergic neurons slows the animal's internal representation of elapsed time, suggesting a novel and non-classical role for midbrain DAergic neurons in time encoding.

Disclosures: S. Soares: None. **B.V. Atallah:** None. **T.S. Gouvêa:** None. **T. Monteiro:** None. **J.J. Paton:** None.

Poster

802. Systems and Behavior

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 802.01/R14

Topic: D.15. Basal Ganglia

Support: Michael J. Fox Fundation

Title: Loss of Gad67 in neurons expressing dopamine Drd1a receptors prevents the development of l-DOPA-induced dyskinesias in a mouse model of Parkinson's disease

Authors: *J.-J. SOGHOMONIAN[1], K. ZHANG[2], C. CHAMMAS[2];
[1]Anat. and Neurobio., [2]Boston Univ. Sch. of Med., Boston, MA

Abstract: L-DOPA-induced dyskinesias are a major detrimental side effect of l-DOPA administration in patients with Parkinson's disease. The objective of this study was to determine the contribution of the Gad67 isoform of the GABA-synthesizing enzyme glutamic acid decarboxylase in striatal neurons on dyskinesias induced by l-DOPA in a 6-hydroxydopamine-mouse model of Parkinson's disease. Mice with a floxed Gad1 exon 2 (Gad1=gene encoding for Gad67) were bred with mice expressing Cre-recombinase under the activity of the promotor for the dopamine Drd1a receptor, which is predominantly expressed in striatal direct pathway neurons, or under the activity of the promotor for Gpr88, an orphan G-protein coupled receptor predominantly expressed in direct and indirect pathway striatal neurons. Mutant mice with a deletion of Gad1 exon 2 in Drd1a or Gpr88-expressing neurons had a prominent decrease in Gad67 levels in the striatum and the substantia nigra but not in the cerebellum or the cerebral cortex, a finding consistent with evidence that these proteins are highly and predominantly expressed in the striatum. Mice with a Gad67 deficiency in Drd1a-expressing neurons were impaired on the pole test and the Rotarod suggesting that a deficit in GABAergic inhibition in the direct pathway impairs motor coordination and balance. In contrast, mice with a Gad67-deficiency in Gpr88-expressing neurons had a performance comparable to control littermates. Gad67-deficient and control littermate mice were lesioned with 6-OHDA in the medial forebrain bundle on one side of the brain. Three weeks post-surgery, mice were injected once daily for 10 days with l-DOPA. Control littermate mice or mice with a Gad67 deficiency in Gpr88-expressing neurons developed abnormal involuntary movements (AIMs) soon after the onset of l-DOPA administration. In contrast, mice with a Gad67 deficiency in Drd1a-expressing neurons did not exhibit AIMs in response to l-DOPA. These finding indicate that Gad67 in direct pathway striatal neurons plays a key role in motor control in the dopamine-intact mice and in l-DOPA-induced dyskinesia in the dopamine-deficient brain. We also conclude that the additional loss of Gad67 in indirect pathway neurons cancels out the effects of Gad67 loss in direct pathway neurons.

Disclosures: J. Soghomonian: None. **K. Zhang:** None. **C. Chammas:** None.

Poster

802. Systems and Behavior

Location: Hall A

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Program#/Poster#: 802.02/R15

Topic: D.15. Basal Ganglia

Support: NSERC Discovery Grant

NSERC CREATE Training Grant

AIHS Polaris Award

Title: Intrinsic choice reflexes in the sensorimotor striatum

Authors: *A. J. GRUBER[1], R. THAPA[2], P. BANKS[2];
[1]Dept. of Neurosci., [2]Univ. of Lethbridge, Lethbridge, AB, Canada

Abstract: The propensity of animals to switch choices immediately after unexpectedly poor reinforcement outcomes is a pervasive strategy across species and tasks. We report here that such lose-switch responding rapidly decays in rats and is blocked by corrupting the negative reward prediction error signal transmitted by dopamine in the sensorimotor striatum. Moreover, we found that decaying lose-switch responding emerges in humans when subjects are given a cognitive load and must presumably rely on motor systems for task performance. These data reveal an important but underappreciated role of motor-related systems in rapid choice adaptation. We propose that this immediate lose-switch responding is aptly described as an instinctual choice reflex due to its predictably rapid decay and ubiquity despite being a sub-optimal strategy in the present task. In addition to solving simple ethological tasks, we speculate that this mechanism could cease animals' current response policy when outcomes are poor so that computationally expensive behavioural control systems can implement an improved strategy.

Disclosures: A.J. Gruber: None. **R. Thapa:** None. **P. Banks:** None.

Poster

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AFSGT Grant

Title: Juvenile onset of stereotypy with loss of BDNF signaling in D1R expressing striatal neurons

Authors: ***M. ENGELN**[1], R. CHANDRA[1], A. LA[2], T.-C. FRANCIS[1], M.-K. LOBO[1]; [1]Anat. and Neurobio., Univ. of Maryland, Baltimore, Baltimore, MD; [2]Univ. of Maryland, Col. Park, College Park, MD

Abstract: Imbalance between D1- vs. D2-receptor containing medium spiny neuron (MSN) basal ganglia output-pathways is implicated in stereotyped disorders including Tourette Syndrome (TS). Surprisingly, there is little information on the molecular role of MSN subtypes in TS or other stereotypy disorders. We have a mouse model carrying a deletion of TrkB (the BDNF receptor) in D1-MSNs (D1-Cre-flTrkB mice), in which a subset of mice display involuntary stereotypic behaviors beginning around 3 weeks of age. Consistent with an impaired GABAergic system in TS, these mice display a decrease in striatal GABA-A subunits accompanied by reduced inhibition in striatal D1-MSNs. We first characterized repetitive behaviors in D1-Cre-flTrkB mice with stereotypy (S), or with no stereotypy (NS), and D1-Cre control mice. Complete turns, head tics, rearing, and grooming are assessed weekly from ages 3 to 8 weeks. Since the transcription factor, early growth response 3 (Egr3) is regulated by BDNF and Egr3 transcriptionally regulates a subset of GABA-A subunits, we are examining striatal Egr3 mRNA in all groups. We found that D1-Cre-flTrkB-S mice display more complete turns at all ages compared to D1-Cre-flTrkB-NS and control mice. D1-Cre-flTrkB-S mice exclusively display head tics, which decline from juvenile to adult ages. Our preliminary data demonstrates decreased Egr3 mRNA in the striatum of D1-Cre-flTrkB mice. To investigate if this change is specific to D1-Cre-flTrkB-S mice we are using D1-Cre-flTrkB-RiboTag mice to measure Egr3 levels in D1-MSNs and chromatin immunoprecipitation to examine Egr3 transcriptional regulation of GABA-A subunits in these mice. In addition, we overexpress Egr3 in D1-MSNs with AAV-DIO-Egr3-eYFP to rescue these stereotyped behaviors. Our findings demonstrate that D1-MSNs through dysfunctional BDNF signaling play a role in juvenile onset of stereotypy behaviors. The enhanced stereotypy behaviors potentially occur through reduced inhibition in D1-MSNs via altered Egr3 regulation of GABA-A subunits. Our ongoing studies can provide novel insight into the cell subtypes and molecular mechanisms underlying stereotypy disorders.

Disclosures: **M. Engeln:** None. **R. Chandra:** None. **A. La:** None. **T. Francis:** None. **M. Lobo:** None.

Poster

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Topic: D.15. Basal Ganglia

Support: ERC Starter Grant

NWO Vidi Grant

Title: Optimizing functional MRI sequences at 7 Tesla for subcortical nuclei

Authors: *B. U. FORSTMANN[1], M. KEUKEN[1], R. TRAMPEL[2], G. DE HOLLANDER[1]; [1]Univ. of Amsterdam, Amsterdam, Netherlands; [2]Max Planck Inst. for Human Cognitive and Brain Sci., Leipzig, Germany

Abstract: The substantia nigra (SN) and subthalamic nucleus (STN) are thought to be important, distinct nodes in a cortico-basal ganglia loop implementing cognitive functions such as perceptual decision-making and cognitive control. The STN is the main target of deep brain stimulation (DBS), a popular and effective treatment of Parkinson's Disease. This treatment can lead to serious side-effects and the underlying mechanisms are not well-understood. Ultra high-resolution functional MRI could help elucidate both the function of the STN in the healthy population, as well as lead to a better understanding of the side-effects of DBS because these might be related to functional subdivisions within the STN. However, deriving a functional MRI signal from these subcortical nuclei remains a challenge. Anatomical specificity requires a very high spatial resolution due to the small size and close proximity of the two nuclei. In addition, the signal-to-noise-ratio is hampered by the fact that the SN and STN show highly elevated concentrations of iron, which lead to greatly reduced baseline T2* values. Also, the nuclei lie deep in the brain, far from, and approximately equidistant to the different receive elements of a multi-channel array coil. The resulting increased g-factor reduces the performance of parallel imaging sequences and ultimately the signal-to-noise ratio in those regions. We present a set of functional imaging studies at ultra-high field (7T), measured while participants performed the stop-signal paradigm. Different spatial resolutions, echo-times, and acceleration factors were acquired in an effort to optimize signal-to-noise ratio and anatomical specificity of functional MRI in the iron-rich human basal ganglia including the SN and STN.

Disclosures: B.U. Forstmann: None. **M. Keuken:** None. **R. Trampel:** None. **G. de Hollander:** None.

Poster

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Topic: D.15. Basal Ganglia

Support: The effect of normabaric hyperoxia treatment on energy metabolism and dopaminergic gene expression in basal ganglia following everetraumatic brain injury in mouse model of C57BL/6J (Account no: 1001/PPSP/813032 Universiti Sains Malaysia).

Title: Normobaric hyperoxia treatment following fluid percussion injury in striatum of mice improved locomotors activity through neuroprotection and enhancement of dopaminergic system

Authors: *S. MUTHURAJU, J. ABDULLAH, M. RAFIQUL ISLAM;
Univ. Sains Malaysia, Kota Bharu, Malaysia

Abstract: Objective: Fluid percussion injury (FPI) is most substantial method to mimic closed traumatic brain injury (CTBI). Majority of accident caused CTBI which leads to increase mortality rates in developing countries. However, sustainable therapeutic approach has not been established yet. Therefore, the present study was designed to evaluate the impact of normobaric hyperoxia treatment (NBOT) on striatum associated locomotors activity and dopamine genes after FPI. Methods: Locomotors activity has been assessed using a new computerized well recognized behavior tool called IntelliCage. Animals were divided four groups such as Group I control (n=15), Group II sham (n=15) (only cannula implanted), Group III FPI (n=15) and Group IV FPI with NBOT (n=15). Animals were habituated in IntelliCage for 4 days following transponder implanted in mice neck region on 5th day. Locomotors activity of all four groups of animals has been assessed for 5 days for 6hr (9am-3pm) before inducing FPI. On 6th day, cannula was implanted on striatum, on 7th day FPI was performed in Group III (kept in normal environment) and IV (immediately exposed to NBOT for 3hr). Locomotors activity was assessed at 1st, 7th, 14th, 21st and 28th days following FPI in IntelliCage for 6hr. At the end of the behavior experiment, neuronal morphology and dopamine receptors (D1 and D2), Dopamine transporter (DAT) and Vesicular monoamine transporter (VMAT) were also assessed. Results: The data suggested that FPI significantly impaired locomotors activity of mice as compared to control and sham in terms of less number of visits in all four corners of IntelliCage in associated with downregulation of dopamine genes. The immediate exposure to NBOT improved locomotors activity in terms of increased number of visits in all four corners as compared to FPI and upregulated dopamine genes and minimized neuronal damage. Conclusion: Taken together these results concluded that normobaric hyperoxia exposure could improve the locomotors activity of mice following fluid percussion injury in striatum through prevent neuronal damage and enhancement of dopaminergic neurotransmission. The present study suggested that NBO treatment could be possible therapeutic approach for improving dopaminergic neurons as well as

locomotors activity following closed traumatic brain injury victims. Key words: Traumatic Brain injury, Normobaric Hyperoxia Treatment, IntelliCage, Locomotors activity, Striatum, Dopamine. E.mail: brainsciences@gmail.com

Disclosures: S. Muthuraju: None. **J. Abdullah:** None. **M. Rafiqul Islam:** None.

Poster

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Topic: D.15. Basal Ganglia

Support: NIA T32 AG20506

Title: Functional imaging of dopaminergic projections in dorsal striatum with single-axon resolution in behaving mice

Authors: *M. HOWE[1,2], D. A. DOMBECK[2];
[1]Neurosci., Northwestern Univ., Chicago, IL; [2]Northwestern Univ., Evanston, IL

Abstract: Dopamine signaling in the striatum has long been recognized as critical for regulating movement on immediate timescales, and for driving learning-related plasticity over extended timescales. Current theories of dopamine function, derived primarily from midbrain electrophysiological recordings in the midbrain SNc and VTA, propose that dopamine neurons homogenously transmit phasic (hundreds of ms) signals to unpredicted rewards or reward-predictive cues. These signals are believed to enhance representations of environmental stimuli or actions that lead to reward, driving future goal-directed learning and behavior. Regulation of ongoing movement, on the other hand, is believed to be enabled by the ongoing tonic or slowly varying (several seconds) firing within these same neurons. Recent electrophysiological and voltammetric recordings in different striatal subregions have called these theories into question, but lack the combination of fine (micron scale) spatial resolution, striatal projection target specificity, and large sampling region necessary to adequately assess functional dynamics across populations of dopamine axons projecting to specific striatal subregions. To overcome these limitations, we have developed a new approach based on two-photon imaging of genetically encoded calcium indicators to measure dynamics across the dopaminergic projection population to dorsal striatum with single axon resolution in behaving mice. We are applying this new imaging method to test existing models of dopamine signaling. Preliminary data suggests that locomotion related signaling may be present within the projection population and may be

separate from the reward signaling projection population. Such a finding would require revisions of current models of the dopamine signaling dynamics in the striatum responsible for movement regulation and reinforcement learning.

Disclosures: **M. Howe:** None. **D.A. Dombeck:** None.

Poster

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Support: NIH MH101697

NIH NS078435

CHDI

Title: Contributions of the globus pallidus to action selection and proactive inhibition

Authors: ***B.-M. GU**, C. LU, S. BIDWELL, J. BERKE;
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Abstract: Basal ganglia networks provide important gating mechanisms that facilitate adaptive behavioral control. This control includes action suppression, which is essential to achieve flexible, non-impulsive behavior. The indirect pathway through the globus pallidus (GP; GPe in primates) is often considered a "No-Go" pathway, but how exactly it contributes to action suppression is not well understood. One proposal (Aron 2011) is that GP contributes to "proactive" behavioral inhibition, also called action restraint. This is manifest as greater preparedness-to-stop, for example in proactive versions of the Stop-signal task. We have started to assess the behavioral functions of GP using precisely-timed optogenetic manipulations in rats. In order to test GP contributions to both action initiation and proactive inhibition, we first developed a modified version of our existing Stop-signal task (Leventhal et al. 2012; Schmidt et al. 2013). Rats initiate trials with a nosepoke, wait for an instructive Go cue (a tone indicating either Go-left or Go-right), but on some trials a subsequent Stop cue (white noise) indicates that they must remain in the initial location. In the modified, proactive version, distinct starting nosepoke locations are associated with different Stop probabilities (0%, 25%, 50%). As intended, on Go-only trials rats show reaction times that scale with Stop probability, indicating that they are appropriately engaging proactive inhibition mechanisms. In our initial optogenetic

experiments we used Arch to briefly reduce GP activity on one side, either just before the Go cue, together with Go cue onset, or just after the Stop cue. So far we have found that GP suppression during Go cue processing interferes with normal contraversive action selection, and analysis of reaction times suggests that this occurs through biasing a competition between ipsiversive and contraversive choices.

Disclosures: **B. Gu:** None. **C. Lu:** None. **S. Bidwell:** None. **J. Berke:** None.

Poster

802. Systems and Behavior

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Support: NIH: NS078435

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NIH: DA032259

CHDI

University of Michigan

Title: Expectations of reward omission selectively modulate striatal fast-spiking interneurons

Authors: *A. MOHEBI[1], J. R. PETTIBONE[1], M. A. FARRIES[1], J. D. BERKE[1,2,3];
[1]Psychology, [2]Neurosci., [3]Biomed. Engin., Univ. of Michigan, Ann Arbor, MI

Abstract: The striatum plays critical roles in motivated decision-making, and in particular dorsal-lateral striatum is thought to store the values of particular actions. These values may be used for selecting and invigorating actions, and are updated by dopamine fluctuations that convey abrupt changes in reward expectation (reward prediction errors). This feedback allows choices to adapt towards the most rewarding options. Striatal medium spiny projection neurons (MSNs) express either lower-affinity dopamine D1 or higher-affinity D2 receptors, so may be differentially sensitive to either rapid increases (D1) or decreases (D2) in dopamine. It has therefore been suggested (e.g. Collins & Frank 2014) that D1-MSN values reflect the recent history of successful outcomes while D2-MSN values reflect the history of reward omissions. Separate storage of these “positive” and “negative” reward expectations may facilitate behavioral

flexibility across different motivational states. We investigated whether separate sets of striatal neurons are indeed modulated by expectations of reward, and of reward omission. We recorded single-units from rat striatum during performance of a trial-and-error (2-armed bandit) left/right choice task. Neurons were separated into presumed MSNs and presumed fast-spiking interneurons (FSIs) based on previously established criteria (e.g. Gage et al. 2010). Firing rates of each cell were regressed against the decision variables of a modified actor-critic reinforcement learning model, which separately tracked positive and negative reward expectations for each action. Unexpectedly, we found that a disproportionate number of FSIs were modulated by negative reward expectation. This modulation was present throughout the trial for some FSIs, but reached a peak (>35% of FSIs) around the moment of choice execution during which FSIs are especially active (Gage et al. 2010). Much less modulation was observed by positive reward expectations, or for MSNs. Although the functional significance of these observations remains to be determined, one possibility is that FSIs are particularly involved in restraining actions that have resulted in worse outcomes than expected.

Disclosures: **A. Mohebi:** None. **J.R. Pettibone:** None. **M.A. Farries:** None. **J.D. Berke:** None.

Poster

802. Systems and Behavior

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Topic: D.15. Basal Ganglia

Support: NIH Grant DA032259

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NIH Grant MH101697

Title: Neuromodulation and adaptive decision-making in frontal cortex and striatum

Authors: *J. R. PETTIBONE[1], A. MOHEBI[1], A. HAMID[2], J.-M. T. WONG[3], R. T. KENNEDY[3], J. D. BERKE[1,2,4];
[1]Psychology, [2]Neurosci., [3]Chem., [4]Biomed. Engin., Univ. of Michigan, Ann Arbor, MI

Abstract: Computational models of adaptive choice typically involve both specific variables, such as the learned values of particular actions, and more global parameters such as reward rate, learning rate or uncertainty. It is widely hypothesized that in the brain such global decision parameters are signaled by neuromodulators such as dopamine, noradrenaline, serotonin and

acetylcholine (e.g. Doya 2002). However, direct evidence for this remains quite sparse. Furthermore, there is evidence that a given neuromodulator may provide different signals, either in distinct subregions that participate in competing behavioral strategies (e.g. dorsal-medial vs. dorsal-lateral striatum) or in distinct yet cooperating brain structures (e.g. prefrontal cortex and dorsal-medial striatum). We have been investigating the computational contributions of neuromodulators to adaptive choice, using microdialysis coupled to HPLC-MS. This method allows us to sample a wide array of neurochemicals simultaneously, each with 1-minute resolution. Samples are taken from rats during performance of a stochastically rewarded two-armed bandit task, and compared to decision parameters estimated using a Bayesian reinforcement learning algorithm. In our initial study we have sampled from the nucleus accumbens and found a selective relationship between dopamine and reward rate, which helps determine motivation to work (engage in activities that are not inherently rewarding, but may lead to rewards). We are currently sampling from other brain regions including medial frontal (prelimbic) cortex and dorsal-medial striatum, to test whether each neuromodulator provides a consistent computational signal.

Disclosures: J.R. Pettibone: None. **A. Mohebi:** None. **A. Hamid:** None. **J.T. Wong:** None. **R.T. Kennedy:** None. **J.D. Berke:** None.

Poster

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Topic: D.15. Basal Ganglia

Support: R01 MH099505-02

Title: Chemogenetic control of motor behavior in the non-human primate: DREADD-mediated silencing of the substantia nigra pars reticulata

Authors: *B. L. AGUILAR, C. ELORETTE, M. N. HUIZENGA, P. A. FORCELLI, L. MALKOVA;
Georgetown Univ., Washington, DC

Abstract: Classic approaches to focal brain manipulation in non-human primates have primarily relied on lesion techniques, and more recently focal microinjections of drugs to transiently suppress neural activity. While these techniques have been enormously informative, the former does not allow for repeated within-subject assessments, and may allow for compensatory

neuroadaptation in the post lesion period. The latter approach minimizes some of these confounds but is technically challenging. Moreover, repeated microinfusions may cause tissue damage. Designer receptors exclusively activated by designer drugs (DREADDs) allow for the selective activation of DREADD-expressing neurons by otherwise inert compounds. Because DREADD constructs may be delivered virally, only a single surgery and brain penetration is needed to produce life-long sensitivity to systemic administration of DREADD-activating compounds (e.g., CNO). While this approach has been extensively deployed in rodents, it remains understudied in primates. Here, we targeted the substantia nigra pars reticulata (SNpr), a key basal ganglia output structure for DREADD-mediated inhibition. We have previously reported (Dybdal et al., 2013, Holmes et al., 2012) that unilateral inhibition of SNpr induces profound locomotor and postural abnormalities, as well as limb dyskinesias. The importance of this structure in movement disorders, coupled with the relative ease of behavioral measures of nigral inhibition led us to select SNpr as a pilot target. We injected AAV-hSyn-HA-M4D(Gi)-IRES-mCitrine into the substantia nigra of 3 macaques during an MRI guided stereotaxic surgical procedure. We allowed a minimum of 1 month post-operative recovery before behavioral testing. Each animal was tested with a series of vehicle injections and at least 3 CNO sessions. The primary behavioral output was contraversive quadrupedal rotations (QR). In each animal, the frequency of QR was increased by CNO administration. A mean 60% increase in rotation rate ($P<0.05$) was observed. Post-mortem histological confirmation of virus injection was performed on two animals. Histological analysis showed sparse labeling within the reticulata and compacta of the SN. Histological assessment of a third subject is underway. A fourth subject is currently in progress using an alternative serotype of AAV to increase neural coverage, as well as dual injection of M4-DREADD and Kappa Opiod Receptor DREADD (KORD) allowing independent silencing of two separate neural populations. These results demonstrate the efficacy of DREADD-mediated silencing in the non-human primate and open the door to further studies employing this methodology.

Disclosures: **B.L. Aguilar:** None. **C. Elorette:** None. **M.N. Huizenga:** None. **P.A. Forcelli:** None. **L. Malkova:** None.

Poster

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Support: NSERC grant no. 2015-05465 to RJB

Title: Inverse incentive learning on the bar test in rats following injection of haloperidol into the nucleus accumbens

Authors: *L. N. SCHIMMEL[1], C. DI PROSPERO[1], R. J. BENINGER[2];
[1]Ctr. for Neurosci. Studies, [2]Ctr. for Neurosci. Studies, Departments of Psychology and Psychiatry, Queen's Univ., Kingston, ON, Canada

Abstract: Inverse incentive learning is the loss by stimuli of their ability to elicit approach and other responses. Repeated pairings of injections of a dopamine (DA) receptor antagonist (e.g., haloperidol) with environmental stimuli gradually reduces their incentive value observed as a loss of motor engagement with the environment. c-Fos results implicate several brain regions including the nucleus accumbens (NAc). We examined the role of the NAc in inverse incentive learning by bilaterally infusing haloperidol and testing rats on the horizontal bar test. During the 13-day training phase paired rats were bilaterally infused with haloperidol (10 μg/0.5 μl/side) into NAc 1 h prior to placing them with their forepaws resting on a horizontal bar in a specific environment. Unpaired control rats were infused with saline and similarly tested. Unpaired rats were centrally injected with haloperidol and paired rats with saline 1 h later in their home cage. On the test day all rats were treated with saline prior to the bar test. The dependent variable was descent latency. Groups did not differ at the beginning of training but the paired group showed progressively longer descent latencies over days while the unpaired group did not. On the saline test day, the descent latency of the paired group was longer than that of the unpaired group. Results implicate the NAc in the neuronal mechanisms underlying inverse incentive learning.

Disclosures: L.N. Schimmel: None. **C. Di Prospero:** None. **R.J. Beninger:** None.

Poster

802. Systems and Behavior

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Topic: D.15. Basal Ganglia

Title: *In vivo* study of thalamic axonal dynamics in layer 1 of mice motor cortex

Authors: *O. P. JAIDAR, C. J. ROOME, M. GARCIA-MUNOZ, Y. NAKANO, B. KUHN, G. W. ARBUTHNOTT;
Okinawa Inst. of Sci. and Technol. Grad. Univ., Okinawa, Japan

Abstract: The Motor thalamus plays a key role in movement control, linking cerebellum and basal ganglia to the cerebral cortex. Large amounts of thlamocortical axons projects to different areas of the cerebral cortex. Axonal processes from ventromedial motor thalamus terminate in layer 1 (e.g. Arbuthnott et al. (1990)Neuroscience, 38, 47-60). However, how the thalamic activity changes during motor behavior is unknown. The main goal of this project is to visualize *in vivo* activity of the axons projecting to layer I of the motor cortex in head-restrained mice under the following conditions: isoflurane anesthesia, awake and following systemic haloperidol (0.6mg/kg, i.p.). All animal experiments were approved by the OIST Institutional Animal Care and Use Committee (IACUC) in an Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC International) accredited facility. To visualize *in vivo* activity of thalamocortical axons to layer 1 a mixture of AAV1/2-hSyn-GCamP6f and AAV1/2-hSyn-TurboRFP viral vectors was delivered directly into the motor thalamus of 21 days old C57BL/6J mice. Two weeks later, a chronic cranial window with a silicon access port was placed over the motor cortex, as previously described (Roome, C.J.& Kuhn, B. 2014, Front Cell Neurosci. 8, 379), and two silver wires were placed next to the window for electrocorticography (ECoG) recordings. After a couple of days of acclimatization in a head restrained configuration, calcium transients of thalamocortical axons on layer 1 and ECoG activity were recorded. A custom-built microscope that combines bright field and two-photon resonant-scanning microscopy (31 frames/s, MOM, Sutter) was used to record calcium transients. Animals were filmed during every experimental condition to check vital signs and track locomotion. Our experimental configuration allowed us to detect different populations of Layer 1 axons. One synchronizes their activity during the spontaneous march of the animal becoming quiet under isoflorane anesthesia, while others synchronize their activity during the anesthesia but not during the march. Interestingly, both of them change their activity under the dopaminergic antagonist.

Disclosures: **O.P. Jaidar:** None. **C.J. Roome:** None. **M. Garcia-Munoz:** None. **Y. Nakano:** None. **B. Kuhn:** None. **G.W. Arbuthnott:** None.

Poster

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Topic: D.15. Basal Ganglia

Support: DA006886

Title: Investigating activity of fast spiking interneurons in dorsolateral striatum

Authors: *J. KULIK, K. COFFEY, A. PAWLAK, M. WEST;
Rutgers Univ., Piscataway, NJ

Abstract: Numerous studies have shown that certain types of striatal interneurons might play a crucial role in selection and regulation of striatal output. Among these, striatal Fast-Spiking Interneurons (FSIs) are parvalbumin positive, GABA-ergic interneurons that constitute less than 1% to the total striatal population. FSIs display a strong medial<lateral distribution gradient across the striatum, which suggests that they are important for regulation of motor functions subsumed within the lateral striatum. It is becoming increasingly evident that these sparsely distributed neurons exert a strong inhibitory effect on Medium Spiny projection Neurons (MSNs), the principal neurons of the striatum. MSNs in lateral striatum receive direct synaptic input from regions of cortex representing discrete body parts. Individual MSNs show phasic increases in activity during touch or movement of specific body parts. In the present study we sought to determine whether FSIs, identified by their electrophysiological properties, display body part sensitivity similar to that exhibited by MSNs in the striatum. Body part sensitivity of individual recorded neurons was assessed using a sensorimotor exam in which each individual body part was stimulated and responses of the neuron were observed and quantified. A large proportion of identified FSIs displayed patterns of activity related selectively to stimulation of a discrete body part. Those patterns of activity were often similar to those that are displayed by typical MSNs in the lateral striatum. Some FSIs displayed patterns of activity different from those described for MSNs, such as a dramatic decrease in firing during movement of the related body part. Together these results serve as evidence that striatal FSIs process information related to discrete body parts and participate in control of motor output by the striatum.

Disclosures: **J. Kulik:** None. **K. Coffey:** None. **A. Pawlak:** None. **M. West:** None.

Poster

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Topic: D.15. Basal Ganglia

Support: DA066886

Title: Exploring body part sensitivity of optogenetically identified D1 and D2 receptor expressing medium spiny neurons in the dorsolateral striatum of the mouse

Authors: *K. COFFEY[1], M. NADER[2], M. WEST[3];
[1]Rutgers Univ., Piscataway, NJ; [2]Psychology, [3]Rutgers, Piscataway, NJ

Abstract: The dorsolateral striatum (DLS) of the mouse is a large structure situated at the base of the forebrain and is associated with a variety of functions including control of voluntary motor movements, sensory-motor integration, procedural learning, and habits. Dysfunction of the dorsal striatum is also associated with a number of diseases such as Tourette syndrome, obsessive-compulsive disorder, psychomotor stimulant addiction, Parkinson's disease, and Huntington's disease. The DLS is thought to be functionally organized in order to support sensorimotor processing. First, the DLS is hypothesized to contain two opposing pathways, defined by their dopamine receptor expression. The D1 pathway, or the “direct” pathway, is thought to be responsible for generating movement while the D2, or the “indirect” pathway, is thought to be responsible for inhibiting movement. Further, the DLS is known to be somatotopically organized, and it has been repeatedly shown to process single body part movements and sensation (Kunzle 1975, 1977, 1978; Selemon and Goldman-Rakic 1985). Moreover, the dorsolateral striatum contains patches of neurons that together represent all parts of an animal’s body (Carelli and West 1991). This is because the DLS receives direct topographical projection from the primary somatosensory and motor cortices. The present study seeks to explore the relationship between these two functional organization schemes. We utilized optogenetics coupled with electrophysiological recordings in the awake behaving mouse to identify D1 and D2 receptor expressing medium spiny neurons (MSNs) in the DLS. We then performed “body exams” in order to determine the body part sensitivity of individual MSNs. Differences or similarities between D1 and D2 neurons will be explored with regards to single body part processing.

Disclosures: K. Coffey: None. **M. Nader:** None. **M. West:** None.

Poster

802. Systems and Behavior

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 802.15/S8

Topic: D.15. Basal Ganglia

Support: Intramural Research Program, NINDS, NIH

Title: Relationship between the cerebellar dentate nucleus, VA/VL and VM thalamus and motor cortex in the generation of high gamma oscillation during L-DOPA-induced dyskinesia in Parkinson’s disease

Authors: *C. DELAVILLE, H. BERMUDEZ CABRERA, A. J. MCCOY, J. R. WALTERS; NIH NINDS, Bethesda, MD

Abstract: The neural mechanisms and circuitry involved in L-DOPA-induced dyskinesia (LID) remain unclear. Recently, high gamma frequency oscillations (70-120 Hz with a distinct peak around 80 Hz), referred to as finely-tuned gamma (FTG) in patients, have been observed in the motor cortex (MCx) and correlated with the emergence of LID in a rodent model of Parkinson's disease (PD). Recent studies suggest that there are also changes in cerebello-thalamo-cortical networks occurring in PD and LID and that continuous cerebellar stimulation has an antidyskinetic effect in PD patients with LID, possibly due to modulation of this pathway (Koch et al., 2007). The cerebellar dentate nucleus (Dn) is an essential structure for the control of movement and sends ascending projections to the cortex via the ventromedial/ventrolateral (VA/VL) thalamus. To investigate the contribution of the Dn and VA/VL thalamus in the generation of high gamma oscillations during LID, we used the hemiparkinsonian rat model and recorded chronic activity in the Dn, VA/VL and ventromedial (VM) thalamus and MCx during LID followed by the local inactivation of the Dn using muscimol. As expected, after dopamine cell lesion, a strong high beta peak appeared in the MCx (4X increase in total power around the peak relative to control) and in the VM (10.7X). However, this 28-36 Hz oscillation was not present in either the Dn or VA/VL (1.2X and 1.2X, respectively). After chronic L-DOPA treatment, a substantial high gamma-FTG-like band appeared in the MCx (18X), VM (16.3X) and modestly in VL (3.2X) but not in Dn (0.9X). As expected, VM thalamus LFPs were coherent with MCx in both the high beta range after dopamine depletion and the high gamma range during LID. In contrast, VA/VL activity was not coherent with MCx in the high beta range but was significantly coherent with the MCx in the high gamma range after chronic L-DOPA treatment. Dn LFP activity was not coherent in the high beta and high gamma ranges with MCx, VA/VL or VM thalamus in any condition. Inactivation of the Dn by local injection of muscimol during LID did not significantly change the effect of L-DOPA on high gamma power and coherence between MCx, Dn, VA/VL or VM. However, this local Dn inactivation during LID significantly decreased the degree of phase locking of VA/VL spikes to their own LFP, filtered between 70 to 120 Hz without affecting the phase locking of VM neurons to their own LFP. These results indicate that the Dn contributes to coordinated VA/VL spiking activity in the high gamma range but does not impact either the expression of LID or high gamma-FTG like activity in the MCx and VM.

Disclosures: C. Delaville: None. **H. Bermudez Cabrera:** None. **A.J. McCoy:** None. **J.R. Walters:** None.

Poster

802. Systems and Behavior

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 802.16/S9

Topic: D.15. Basal Ganglia

Support: Intramural Research Program, NINDS, NIH

Title: Does the parafascicular nucleus participate in transmission of oscillatory activity in motor circuits in hemiParkinsonian rat?

Authors: *E. BRAZHNIK, N. NOVIKOV, A. J. MCCOY, J. R. WALTERS;
Neurophys/Pharmacol Section, NIH NINDS, Bethesda, MD

Abstract: Exaggerated beta range oscillations in the basal ganglia are a prominent characteristic of Parkinson's disease (PD). However, the neural mechanisms and circuitry underlying these oscillations remain unclear. The motor thalamus receives inhibitory input from basal ganglia and transmits activity to the motor cortex (MCx), and is implicated in the control of movements. We observed that loss of dopamine is associated with robust increases in high beta range local field potential (LFP) oscillations in the ventromedial thalamic nucleus (VM) (Brazhnik et al. SfN 2011). The parafascicular thalamic nucleus (Pf), which receives inputs from the basal ganglia, cortex and cerebellum, provides feedback to the subthalamic nucleus and striatum, and may also contribute to the exaggerated oscillatory activity in the basal ganglia-thalamocortical circuit in PD. The present study explores this hypothesis. Electrodes were implanted into the Pf, substantia nigra pars reticulata (SNpr), dorsal striatum and MCx in in one group of rats and into the VM, SNpr and MCx in a second group. LFPs and spike activity were recorded in rats during epochs of rest and walking on a circular treadmill before and after 6-OHDA-induced dopamine cell loss and during L-DOPA-induced dyskinesia. Recordings from electrode bundles in the ventrolateral part of Pf showed very modest, but noticeable (from selected wires) 30-36 Hz range activity and low coherence with SNpr and MCx LFPs on day 21 postlesion. Pf spiking showed modest synchronization with local LFPs in the beta range (24 % spike trains were significantly correlated after dopamine cell lesion relative to 12% in control), but not with MCx and striatal LFPs. In contrast, recordings from the VM showed a 3-5 fold increase in VM LFP power and VM LFP coherence with both MCx and SNpr in the 30-36 Hz range after dopamine loss, relative to controls. Along with this, VM spikes were highly synchronized with both thalamic and cortical LFPs (82% and 65% spike trains, respectively). Chronic treatment with L-DOPA evoked dyskinesia and significantly increased power in the high gamma band (90-120 Hz, peak ~100 Hz) in all recordings from MCx and VM, but only in 15% of recordings from Pf. In addition to observations that inhibition of the VM by muscimol reduced both high beta and L-DOPA-induced high gamma rhythms in the basal ganglia-thalamocortical loop (Brazhnik et al. SfN 2011, 2013), these results support the view that the enhanced beta oscillations which emerge following dopamine loss are generated in the basal ganglia-thalamocortical network with the VM, not the Pf, as a critical element of the circuit.

Disclosures: **E. Brazhnik:** None. **N. Novikov:** None. **A.J. McCoy:** None. **J.R. Walters:** None.

Poster

802. Systems and Behavior

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 802.17/S10

Topic: D.15. Basal Ganglia

Support: Intramural Research Program, NINDS, NIH

Title: Ventromedial thalamus is critical for expression of cortical narrow band high gamma oscillations but not L-DOPA-induced dyskinesia in hemiParkinsonian rats

Authors: *K. B. DUPRE, C. P. DODGE, C. DELAVILLE, E. BRAZHNIK, N. I. NOVIKOV, J. R. WALTERS;
Neurophys/Pharmacol Sec, NIH NINDS, Bethesda, MD

Abstract: Chronic treatment with the dopamine (DA) precursor levodopa (L-DOPA) in Parkinson's disease (PD) frequently causes severe motor complications known as L-DOPA-induced dyskinesia (LID), the causes of which are not fully understood. Interestingly, robust increases in cortical narrow band high gamma activity, also referred to as finely-tuned gamma, appear in PD patients following L-DOPA and coincide with LID in hemiparkinsonian rats. As L-DOPA is thought to reduce basal ganglia inhibitory output to the thalamus, a logical hypothesis is that reduction of this inhibition would increase excitatory thalamic output to the motor cortex, inducing exaggerated cortical high gamma and, in turn, dyskinesia. However, infusion of the GABA A receptor agonist muscimol into the ventromedial (VM) thalamus prior to systemic L-DOPA prevented the expression of cortical narrow band high gamma activity without affecting LID (Brazhnik et al. 2013 SfN abstract). To further explore this apparent dissociation between thalamocortical high gamma activity and LID, rats with unilateral DA cell lesions were subsequently injected with L-DOPA once daily for 7 days to induce stable dyskinesia. LFPs and neuronal activity were recorded from chronically implanted electrodes in the motor cortex and cannulatrodes in the VM thalamus, which enabled monitoring of VM thalamus spiking and LFP activity following local drug infusions. Similar to our previous work, L-DOPA caused dramatic increases in narrow band high gamma (70-110 Hz with a peak ~90 Hz) LFP power in, and coherence between, the motor cortex and VM thalamus in conjunction with dyskinesia. Muscimol (but not saline) infused into the VM thalamus during peak dyskinesia eliminated high gamma activity in both brain regions without impacting dyskinesia. Phase locking of VM thalamus spikes to both their own and motor cortex LFPs in the high gamma range was increased

during dyskinesia (when high gamma power was high) and decreased following muscimol (when high gamma power was low). In contrast, phase locking of motor cortex pyramidal neurons to their own LFP was increased following muscimol when high gamma LFP power decreased. Our findings suggest that the VM thalamus is generating and/or propagating exaggerated high gamma activity in the motor cortex during LID. However, this thalamocortical high gamma activity does not appear to be responsible for causing dyskinesia. Furthermore, our results question the assumption that the thalamus is a critical nucleus for precipitating the expression of LID. Thus, the functional correlate of narrow band high gamma activity during LID in PD, as well as the mechanisms responsible for dyskinesia, remain elusive.

Disclosures: K.B. Dupre: None. **C.P. Dodge:** None. **C. Delaville:** None. **E. Brazhnik:** None. **N.I. Novikov:** None. **J.R. Walters:** None.

Poster

802. Systems and Behavior

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 802.18/S11

Topic: D.15. Basal Ganglia

Support: CONACyT

James S. McDonnell Foundation

Title: Long-term effects in cortical evoked potentials in response to GPi-DBS in childhood generalized dystonia

Authors: *E. ARGUELLES[1], N. H. BHANPURI[2], M. BERTUCCO[1], T. D. SANGER[1]; [1]USC, Los Angeles, CA; [2]NorthShore Univ. HealthSystem, Skokie, IL

Abstract: Dystonia is a movement disorder characterized by involuntary muscle contractions and abnormal postures. Dystonic symptoms have been associated with basal ganglia dysfunction and increased cortical excitability. Deep brain stimulation of the internal segment of the globus pallidus (GPi-DBS) is a common treatment for severe dystonia, despite an incomplete understanding of its mechanisms of action. We hypothesize that GPi-DBS reduces cortical excitability, disrupts the abnormal information flow through the pallidothalamocortical loop, and reduces transcortical long-latency stretch reflexes. An essential component of this hypothesis is that DBS has an effect on cortex that could be mediated by anterograde trans-synaptic pathways from GPi via thalamus. We measure the effects of DBS on cortical activity by recording changes

in scalp EEG evoked by 9hz DBS. We previously showed that the DBS evoked potentials (DBSEPs) amplitude in contralateral paracentral leads at 20msec after stimulation correlates with clinical improvement in children with primary and secondary generalized dystonia, and they may therefore provide a measurement of the modulatory effect of GPi-DBS in cortex. Because clinical effects often occur after months of starting stimulation, we now investigate whether progressive changes in efficacy are reflected in progressive changes in the transmission of DBS pulses from GPi to cortex. We recorded DBSEPs for 8 pediatric patients with generalized dystonia at 1, 3, 6 and 12 months after DBS implantation. We analyze the cortical activity in response to GPi-DBS by examining the DBSEPs for different stimulation contact pairs and voltages. DBSEP amplitude is highly sensitive to variations in scalp impedances, therefore we use the DBSEP voltage gain (the rate of increase in evoked potential amplitude relative to increase in stimulation voltage) as a more reliable indicator of how well a stimulation contact pair can selectively recruit neurons in and around GPi that have connections to cortex. Our results indicate that while the cortical response to GPi-DBS is larger for the most effective contact pairs, changes in DBSEP voltage gain over time do not correlate with overall clinical improvement. Indeed, for a subgroup of patients that showed clinical improvement of motor function after one year of implantation, DBSEP voltage gains remained low throughout the study. This suggests that changes over time in the effect of DBS are not mediated by changes in conduction of stimulation from GPi to cortex. Other mechanisms, such as plastic changes within the basal ganglia or cortex, must therefore be the cause of the gradual improvement in dystonia following GPi DBS.

Disclosures: **E. Arguelles:** None. **N.H. Bhanpuri:** None. **M. Bertucco:** None. **T.D. Sanger:** None.

Poster

802. Systems and Behavior

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 802.19/S12

Topic: D.15. Basal Ganglia

Support: Klingenstein-Simons Fellowship

NARSAD Young Investigator Grant

NSF BRAIN-EAGER Award

Title: Testing the role of ventral tegmental area inputs to Area X in vocal plasticity

Authors: *L. XIAO, G. CHATTREE, T. F. ROBERTS;
Dept. of Neurosci., Univ. of Texas Southwestern Med. Ctr., Dallas, TX

Abstract: Brain circuits associated with the basal ganglia are involved in the learning and execution of a wide range of behaviors. In songbirds, the output of the basal ganglia pathway plays an important role in implementing changes in vocal behavior during song learning. Further, this circuit plays a critical role in biasing motor output in response to reinforcement learning paradigms, such as those using pitch contingent disruptive auditory feedback. A longstanding, idea is that the ventral tegmental area (VTA) provides a reinforcement signal that helps instruct adaptive changes in song performance through its projection onto the striatopallidal portion of the song circuit (Area X). We have begun to test this idea using pitch contingent optogenetic manipulation (pCOM) of VTA axon terminals in Area X. We find that pCOM of VTA axon terminals in adult zebra finches is sufficient to elicit graded changes in the pitch of an optogenetically targeted syllable over the course of hours and days. Pitch contingent optogenetic silencing of VTA terminals result in changes to syllable pitch that function to minimize optogenetic silencing of the circuit. This adaptive shift in syllable pitch away from frequency ranges being targeted by light are reminiscent of the behavioral changes associated with pitch contingent disruptive auditory feedback. In contrast, pitch contingent optogenetic stimulation of VTA terminals elicit changes in song syllables that function to maximize optogenetic stimulation. For example, targeting optogenetic stimulation only to the lower pitch 'registers' of a syllable results in a significant decrease in the mean pitch over the course of hours and days. These preliminary findings support the idea that VTA provides a positive valence signal to Area X important for instructing vocal plasticity.

Disclosures: L. Xiao: None. **G. Chattree:** None. **T.F. Roberts:** None.

Poster

802. Systems and Behavior

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 802.20/S13

Topic: D.15. Basal Ganglia

Title: Effects of enriched housing on the expression of novelty-shuttling induced Fos-LIke Immunoreactivity in the cingulate cortex and basal ganglia

Authors: *W. M. STRUTHERS, S. P. MEDRANO, K. ANSELL;
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Abstract: Previous research has indicated that environmental enrichment (EE) that includes complex housing conditions with varied objects provides enhanced sensory, motor, cognitive and social opportunities that influence brain development and behavioral responses. In our lab this has been demonstrated in a previous study where young male rats housed in enriched conditions display reduced novelty-induced Fos-Like Immunoreactivity (FLI), a marker for neuronal activation. Novelty-shuttling is the process of placing animals in repeated novel environments, and the cingulate cortex and basal ganglia have been implicated as brain regions involved in the processing of and response to novel challenges. While much of the research on environmental enrichment targets young animals, little has been done to investigate its impact on adult animals. In this study adult male rats were housed in a Marlau cage for 5 weeks with the enriched housing conditions varied every 3-4 days, or in standard housing conditions with a single cage-mate (SH). At the end of this time frame all animals were placed through a novelty shuttle procedure (30 minutes in an open field with three novel objects, followed by 30 minutes on an Barnes Maze) and then placed in a holding cage for one hour. They were then perfused and their brains processed for FLI. There was a significant increase in novelty shuttling induced FLI in both groups when compared to non-Novelty Shuttled controls. This increase was tempered in the number of cells displaying FLI in the striatum and cingulate cortex of EE males when compared to SH controls. These results suggest that enriched environment can impact adult neural responses in addition to that seen in early development.

Disclosures: **W.M. Struthers:** None. **S.P. Medrano:** None. **K. Ansell:** None.

Poster

802. Systems and Behavior

Location: Hall A

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Topic: D.15. Basal Ganglia

Support: CONACyT Grant 236836

PAPIIT Grant IN201214-26

Title: The timing mechanism in the hundreds of milliseconds is disrupted by a D2 agonist

Authors: ***K. YC**, L. PRADO, H. MERCHANT;
Cognitive Neurobio. LAB-B15, Inst. de Neurobiologia, UNAM, Queretaro, Mexico

Abstract: Studies in rodents and humans have shown that the dopaminergic system is deeply involved in the perception and production of time intervals in the range of seconds. For example, time is overestimated or underestimated in response to the administration of D2 agonists or antagonists, respectively. However, little it is known about the role of D2 in the milliseconds range. Thus, in the present study we analyzed the effect of systemic administration of a D2 agonist on the tapping behavior of Rhesus monkeys performing a Tapping Synchronization Task (ST), and a serial reaction time control task (CT). In each ST trial, the monkeys synchronized their tapping with a metronome to produce five isochronous intervals, and seven target intervals (350-950ms) were presented pseudorandomly. We measured the variability and accuracy of the produced intervals, as well as the stimulus-response asynchronies. We found that dose-dependent increase temporal variability with the D2 agonist (quinpirole), with a complete loss of the scalar property of interval timing at the largest dose (0.05mg/kg). These effects were accompanied with a dose-dependent switch from under- to overestimation of the produced intervals. In addition, stimulus-response asynchronies showed a large increase at the largest dose of quinpirole. In contrast, during the CT the reaction times were not affected by the systemic administration of the D2 agonist. These results suggest that the D2 receptor system is involved in temporal processing in non-human primates, where high systemic doses the quinpirole profoundly disrupts the timing mechanism governing the tapping synchronization to a sensory metronome. The present data support the notion that high levels of D2 agonist produce a change from a time-predicting to a stimulus-reacting behavior during the ST.

Disclosures: **K. Yc:** None. **L. Prado:** None. **H. Merchant:** None.

Poster

803. Finger and Grasp Behavior and Kinematics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 803.01/S15

Topic: D.17. Voluntary Movements

Support: F.R.S.-FNRS (CR) 1.B.087.15F (Belgium)

Title: Anticipatory grip force adjustments as an emerging feature of coordinated feedback control

Authors: ***F. CREVECOEUR**[1], J.-L. THONNARD[1], P. LEFEVRE[1], S. H. SCOTT[2]; [1]Univ. Catholique de Louvain, Louvain-la-Neuve, Belgium; [2]Queen's Univ., Kingston, ON, Canada

Abstract: Suppose that someone bumps into your arm at a cocktail party while you are holding a glass of wine. Such perturbation will engage rapid upper-limb motor responses including the stretch reflex (~20ms) followed by sophisticated, goal-directed feedback responses (long-latency, ~50ms-100ms; early voluntary, >100ms). While such responses can rapidly compensate for the perturbation, it is also clearly desirable in this context that they do not destabilize the grip or spill the wine. Whether and how grip force control during object manipulation is coupled with upper-limb feedback responses to mechanical perturbations remains unknown. We investigated this issue by applying mechanical perturbations on the upper limb of healthy humans while asking them to hold an object stable between their thumb and index fingers (precision grip). We used a perturbation paradigm known to elicit robust and important modulation of upper-limb muscle responses dependent on whether the perturbation pushes the hand towards or away from the goal target. We leverage this paradigm in the context of object manipulation to measure the moment when feedback control of grip force reflects knowledge of upper-limb motor commands. Surface recordings of muscle responses highlight coordinated upper-limb and grip feedback responses in ~60ms. Importantly, target-dependent modulation of muscle responses was observed at the same time in upper-limb and hand muscles. The simultaneous expression of flexible feedback in shoulder and hand muscles cannot be explained by the hypothesis that grip force results from forward models predicting the consequences of motor commands, as this framework implies measurable delays between target-dependent modulation in shoulder and hand muscles (15-20ms). Instead, our results suggest that apparently predictive grip force control is also partially mediated by simpler coordination of motor systems embedded in the feedback control policy.

Disclosures: F. Crevecoeur: None. **J. Thonnard:** None. **P. Lefevre:** None. **S.H. Scott:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BKIN Technologies, Kingston, Canada.

Poster

803. Finger and Grasp Behavior and Kinematics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 803.02/S16

Topic: D.17. Voluntary Movements

Title: Texting on the go: Multi-muscle activation patterns during a dual-task performance

Authors: *P. K. ACHARYA, A. AMEDEE, J. AMEDEE, S. A. WINGES;
Kinesiology, Louisiana State Univ., Baton Rouge, LA

Abstract: Since the first mobile phone prototype was unveiled in 1973 it has become an increasingly integral part of the modern society with more than 6 billion users with applications including video calling, internet browsing, reading, and texting. Most common among young adults, the average number of text messages sent per day often exceeds 100 on average. Texting is a repetitive tapping task accomplished by precise tapping of the thumb(s) using a one- or two-handed method. Text messages are commonly composed while people sit, stand, or walk and require that the thumb make precise dynamic combinations of flexion/extension, abduction/adduction and rotation movements to move across the keypad. Precisely coordinated patterns of muscle activation are necessary to move the thumb while maintaining hand and arm posture during this task. The purpose of this study was to compare multi-muscle activation patterns of the upper limb during a texting task while subjects were standing or walking on a treadmill. The specific hypothesis was that muscles used to stabilize the arm and hand posture to hold the phone would be affected by walking in both the amplitude and temporal domain while no change would occur in intrinsic thumb muscles. Ten healthy college students performed a one-handed texting task using iPhone 3GS. The task incorporated four different repetitive sequences of taps that spanned the texting keyboard, a pangram sentence, and a short phrase more likely to be sent as a text message. Kinematics of the thumb and whole body movement were recorded along with activity from 12 different muscles: abductor pollicis brevis, flexor pollicis brevis, first dorsal interosseous, adductor digiti minimi, extensor pollicis longus, extensor carpi radialis, flexor carpi radialis, extensor carpi ulnaris, biceps brachii, triceps brachii, medial deltoid, trapezius. Subjects were capable of performing the tasks with minimal errors. Accuracy i.e. whether the correct text symbol registered, was not adversely affected by walking on the treadmill and in several cases, subjects had fewer errors while walking on the treadmill compared to standing. Thus the repetitive stepping motion of the treadmill appeared to improve their performance. Differences between in the magnitude of muscle activity were observed for all muscles including the intrinsic thumb muscles during the typing tasks. However the nature of the change i.e., whether walking resulted in increases or decreases in magnitude between standing and walking, varied among subjects. Proficiency was one factor that may have contributed to the differences between subjects but could not explain the difference completely.

Disclosures: **P.K. Acharya:** None. **A. Amedee:** None. **J. Amedee:** None. **S.A. Winges:** None.

Poster

803. Finger and Grasp Behavior and Kinematics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 803.03/S17

Topic: D.17. Voluntary Movements

Support: Rackham Graduate Student Research Grant

Title: Sense of effort: right and left hand sensitivity to proprioceptive feedback

Authors: *Y. ACOSTA-SOJO, B. J. MARTIN;
Univ. of Michigan, Ann Arbor, MI

Abstract: The contribution of sensory feedback to the sense of effort is still debated. A recent study indicated that in a contralateral force-matching task the influence of reference hand vibration was significant for left hand matching of the right hand reference force. However, this effect was negligible when matching in the reverse condition. In addition, a difference in muscle proprioceptive sensitivity between males and females has been observed in another study. Hence, the aim of the study was to understand the sensitivity of the left and right hand sensory systems to vibration induced changes in force control and correlated changes in electromyographic (EMG) activity. Ten strongly right-handed young adults (5 males and 5 females, aged matched), free from any neurological disorders, participated in this pilot study. In this experiment, participants were asked to grasp fixed horizontal cylinders instrumented with strain gauge transducers and exert 20% of their maximum voluntary contraction (MVC) force with the right or left hand. It was required to establish the reference force level and maintain that force for about 12 seconds with or without visual feedback of the force level. Five seconds after stabilization of the exertion a 60 Hz vibration was applied to the distal tendons of the finger flexor muscles. EMG activity was recorded from each hand finger flexor muscles and normalized to each hand 100% MVC. Changes in force and EMG activity were quantified for each hand. The preliminary results show that the vibration-induced increase in EMG activity is significantly greater for the left than the right hand. This increase tends to be greater for females than males, however it did not reach significance as the number of subjects in each group is still small. These results suggest that the gain of the sensory system is greater for the left than right hand, which confirms previous results concerning position sense.

Disclosures: Y. Acosta-Sojo: None. **B.J. Martin:** None.

Poster

803. Finger and Grasp Behavior and Kinematics

Location: Hall A

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Topic: D.17. Voluntary Movements

Support: NIH grant NS-035032

NIH grant AR-048563

Title: Task specific stability of abundant systems: structure of variance and motor equivalence

Authors: *D. J. MATTOS[1], G. SCHÖNER[2], V. ZATSIORSKY[3], M. LATASH[3];
[1]Kinesiology, Penn State Univ., State College, PA; [2]Inst. für Neuroinformatik, Rühr Univ. Bochum, Bochum, Germany; [3]Dept. of Kinesiology, The Pennsylvania State Univ., University Park, PA

Abstract: Task specific stability allows reorganizing elements after perturbations, while being motor-equivalent with respect to values of salient performance variables. Our main goal was to test a hypothesis that self-triggered transient changes in performance of a steady-state task would result in motor equivalence. A secondary goal was to estimate effects of removing visual feedback on the amount of reorganization of motor elements. Healthy subjects performed two variations of a four-finger pressing task requiring accurate production of total force (FTOT) and moment (MTOT). In the Jumping-Target task, a sequence of target jumps induced transient changes in either FTOT or MTOT. In the Step-Perturbation task, the index finger was lifted by 1 cm for 0.5 s using the "inverse piano" device. Visual feedback could be frozen for one of these two variables in both tasks. Deviations in the space of finger modes (hypothetical commands to individual fingers) were quantified in directions that did not change FTOT and MTOT (ME component) and in directions that changed FTOT and MTOT (nME component). The changes in performance led to an increase in both the ME and nME components. After the sequence of target jumps leading to the same FTOT; MTOT combination, the changes in finger modes had a large ME component. Without visual feedback, a large increase in the nME component was observed without consistent changes in the ME component. Results from the Step-Perturbation task were qualitatively similar. These findings suggest that both external perturbations and purposeful changes in performance trigger a reorganization of elements of an abundant system, leading to large ME motion. These results are consistent with the principle of motor abundance corroborating the idea that a family of solutions is facilitated to stabilize values of important performance variables.

Disclosures: D.J. Mattos: None. **G. Schöner:** None. **V. Zatsiorsky:** None. **M. Latash:** None.

Poster

803. Finger and Grasp Behavior and Kinematics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 803.05/S19

Topic: D.17. Voluntary Movements

Title: "Time" as a sensorimotor control problem: performance limits of human auditory--motor entrainment

Authors: *E. W. SAMSON[1], R. W. NICKL[2], M. M. ANKARALI[3], N. J. COWAN[3];
[2]Biomed. Engin., [3]Mechanical Engin., [1]Johns Hopkins Univ., Baltimore, MD

Abstract: To living systems, time is a hidden state (Ankarali 2014; Carver 2013). It is therefore remarkable how effectively animals -- particularly humans -- can synchronize to auditory and other external cues. This requires a nervous system that can both model the environment (Wolpert 1995) and, in the presence of variability, use feedback control to correct timing errors (Repp 2005). To study how humans use feedback control to entrain to a metronome, we designed a virtual-reality sensorimotor synchronization task. The metronome consisted of auditory cues (10 ms pulses at approx. 3500 Hz), with a base inter-pulse interval of 0.3 s. Experiments consisted of trials where temporal "jitters" were imposed on the metronome. Participants held the handle of a user control device ("haptic paddle") and tapped on virtual haptic wall that imitated tapping on a tabletop. We identified tapping events from reaction forces applied to the hand by the wall. Jitters consisted of single- or sum-of-sinusoid variations of timing with amplitudes of 20 ms at each frequency. Seven frequencies were investigated between 0.06 Hz and 1.5 Hz. These jitters allowed us to perturb the metronome in a structured way, yet resulted in jitter sequences that seemed random (particularly in sums of sines) to subjects during the experiment. Both metronome jitters and user "tap" signals were recorded in real time. We estimated the entrainment controller using system identification methods (Ljung 1999), taking inputs as applied jitters, and outputs as deviations of tapping times. We characterized the controller by computing discrete-time frequency response functions from the discrete Fourier transforms of the input and output signals (Roth 2011). Humans respond most strongly to slowly varying auditory signals and responses were consistent across individuals up to 1.5 Hz. Sensorimotor bandwidth was approximately 0.5 Hz. A comparison of estimates from single-sine and sum-of-sine jitter perturbations suggests that the controller is quite linear at low frequencies, consistent with our hypothesis. Second-order transfer functions provide a good approximation to frequency responses, implying that a subject's current response depends on behavior in previous cycles, i.e. multiple jitters may be kept in working memory to plan the next tapping time. This tapping paradigm is a potentially valuable method to study inherent timekeeping because the movement is already learned (thus adaptation is unnecessary), it requires relatively simple movements that generate reduced motor noise, and the mechanical system (the "haptic paddle") can be modeled as possessing a single degree of freedom.

Disclosures: E.W. Samson: None. **R.W. Nickl:** None. **M.M. Ankarali:** None. **N.J. Cowan:** None.

Poster

803. Finger and Grasp Behavior and Kinematics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 803.06/S20

Topic: D.17. Voluntary Movements

Support: NSERC

Title: Pantomime hand-to-mouth movements suggest different sensory control systems mediate arm transport versus mouth shaping during feeding

Authors: *J. M. KARL[1], D. J. QUINLAN[1], K. M. STUBBS[1], I. Q. WHISHAW[2], J. C. CULHAM[1];
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Abstract: Pantomime reach-to-grasp movements are kinematically different from real visually-guided reach-to-grasp movements. These differences may be due, at least in part, to the inefficient coordination of arm and hand movements in the absence of online visual guidance. Withdrawing the hand to place an object in the mouth is a natural and common movement; however, it differs from other reaching actions in that it develops exceptionally early, relies almost entirely on somatosensory guidance, and may be mediated by a single cortical circuit that controls the arm, hand, and mouth. Given these differences, we hypothesized that hand-to-mouth movements may not be subject to the same real vs. pantomime dissociation as visually-guided reach-to-grasp movements. The present study used frame-by-frame video analysis and linear kinematics to analyze hand and mouth movements as participants withdrew the arm and hand to place either real or imagined food items into the mouth for eating. Preliminary results indicate that aspects of arm transport: trajectory, duration, and peak velocity are similar regardless of whether the hand-to-mouth movement is real or pantomimed. Mouth aperture also consistently scales to the size of the food item, but is smaller in the pantomime condition and reflects the smaller hand aperture initially used to grasp imaginary compared to real food items. The results suggest that different sensory control systems mediate arm transport (proprioception) versus mouth shaping (manual haptics) during both real and pantomime feeding actions and thus, the neural substrates that support the two may be at least partially dissociable.

Disclosures: **J.M. Karl:** None. **D.J. Quinlan:** None. **K.M. Stubbs:** None. **I.Q. Whishaw:** None. **J.C. Culham:** None.

Poster

803. Finger and Grasp Behavior and Kinematics

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Topic: D.17. Voluntary Movements

Support: NSF Grant EFRI-1137172

Title: Arm geometric properties contribute to the non-uniform arm position sense across a horizontal workspace for both sighted and visually-impaired subjects

Authors: *K. OH[1,2], B. I. PRILUTSKY[1,2];
[1]Applied Physiol., [2]Ctr. for Human Movement Studies, Georgia Inst. of Technol., Atlanta, GA

Abstract: It has been reported that the precision of arm position sense is non-uniform across a horizontal workspace. The reasons for this non-uniformity are poorly understood. Since the muscle spindles are major contributors to arm position sense and because the non-linear geometric transformation from small changes in hand position to changes in joint angles (and thus in spindles' length) depends on arm posture, we hypothesized that (1) the geometric arm properties could contribute to the non-uniform precision of arm position sense and (2) this contribution would be similar between individuals with normal and impaired vision given their similar arm geometry. To test the first hypothesis, we conducted a Jacobian-based geometric analysis of a plane, two-segment kinematic chain representing the human arm. The geometric analysis revealed theoretical distributions of the precision error of hand position for any given arm configuration. The predicted precision error distributions were nearly orthogonal to the experimentally measured arm stiffness ellipses (Flash, Mussa-Ivaldi, 1990). The analysis also predicted the non-uniformities in arm position sense reported in the literature, thus supporting the first hypothesis. To test the second hypothesis, we measured precision of hand and joint angle position sense in two groups of right-handed subjects: normal vision group (n=10) and visually-impaired group (n=7). In the first experiment, a robot moved the subject's right hand to one of four targets in random order, and the subject matched the joint angles of the left arm to those of the right arm. In the second experiment, the subject matched the hand movement distance and direction from the initial position. The experimental distributions of the precision error for 4 targets were qualitatively similar to the predicted distributions regardless of the tasks and groups of subjects. Also, the direction of the maximum precision error was not statistically different between the two groups of subjects, whereas the magnitude of error was greater in the visually-impaired group. Thus, it can be concluded that arm geometric properties contribute substantially to the non-uniform precision of arm position sense across the horizontal workspace in individuals with normal and impaired vision, and that the direction of the maximum precision error depends on arm geometry. The larger precision errors in arm matching tasks in visually-

impaired individuals might indicate a contribution of visual experience in the precision of arm position sense.

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Poster

803. Finger and Grasp Behavior and Kinematics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 803.08/T2

Topic: D.17. Voluntary Movements

Title: Neuromuscular control in Clarinetists: does thumb-rest position matter?

Authors: *S. A. WINGES[1], K. E. YOUNG[2];
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Abstract: Repetitive static loading has been linked to cumulative overuse injuries. This is of particular importance to musicians whose skill relies on properly supporting their instrument during practice and performance. The resulting musculoskeletal injuries tend to be lateralized for instruments where one arm is predominately responsible for instrument support. Clarinet players support their instrument with the right-hand thumb. Although the Clarinet only weighs ~0.9 kg, the cumulative static loading can cause discomfort in the thumb, wrist, elbow, and shoulder that may evolve into severe overuse injury and debilitating pain throughout the right upper limb. There is a debate among clarinet pedagogues, instrument makers, and the medical community about the most ergonomic position for the thumb rest. To date, no quantitative research has been conducted on the muscular component of this issue. The purpose of this study was to address the impact of thumb rest position on the neuromuscular control of clarinet playing. Surface electromyographic (EMG) recordings of superficial muscles that control the right thumb, wrist, and arm were taken during held note and finger exercises using three different thumb-rest position heights. We hypothesized that a high thumb-rest position would result in a significantly different balance of muscle activity than normal and low thumb-rest positions and that hand size would be a significant factor on muscle activity. Twenty clarinetists (13 female, 26.2 ± 9.578

years old) were divided into groups by hand size (16.54 ± 8.33 mm long) and experience level (12 students, 8 professionals). They performed ten held notes and ten exercises on each of the three thumb-rest positions with five minute breaks between. The notes and exercises were chosen to be inclusive of specific elements of playing. There were significant main effects of rest position on the amplitude of muscle activity recorded from the biceps brachii, abductor pollicis brevis, abductor pollicis longus, extensor carpi radialis and flexor carpi ulnaris. Main effects of hand size on EMG were limited to the triceps brachii. Opposing muscles had contrasting patterns of activation regardless of hand size; therefore, there is no conclusive evidence that altering the standard position for thumb rests would be beneficial everyone, although on a case-by-case basis it may be useful. Interactions between variables such as the exercise, thumb-rest position, and hand size enrich the understanding of the biomechanics of clarinet playing.

Disclosures: S.A. Winges: None. **K.E. Young:** None.

Poster

803. Finger and Grasp Behavior and Kinematics

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Program#/Poster#: 803.09/T3

Topic: D.17. Voluntary Movements

Support: NIH Grant R01HD059783

Title: Interlimb Asymmetries are attenuated in unsupported vs supported reaching movements

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Abstract: Our previous studies have elaborated substantial asymmetries in motor performance between the dominant and non-dominant arms of healthy adults, which have been extended to the hemispheres through studies in stroke patients. Whereas the dominant hemisphere appears specialized for predictive control associated with fast, efficient, and smooth trajectories, the non-dominant arm appears specialized for impedance control that often leads to increased final position stability and accuracy. We now test whether these differences are altered by the dynamic context of supporting the arm against gravity. We propose that this condition results in increased stiffness, which can enhance impedance control for the non-dominant arm, as well as reducing the effect of intersegmental dynamics on asymmetries. Healthy young volunteers performed unimanual dominant and nondominant arm reaching movements under two

conditions: 1) With the arm supported by an air-sled, which removed the effects of gravity and 2) With the arm unsupported. Our preliminary results support the prediction that interlimb differences in coordination and accuracy are reduced under 3-D reaching conditions. Furthermore, consistent with our hypothesis, non-dominant arm movements achieved the final position with greater accuracy under 3-D conditions, as compared with 2-D conditions.

Disclosures: R.L. Sainburg: None. **J.E. Schaffer:** None.

Poster

803. Finger and Grasp Behavior and Kinematics

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Topic: D.17. Voluntary Movements

Support: NIH Grant R03HD074870-02

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Title: Modifying multi-muscle coordination by targeted assistance of hand muscles

Authors: *S. LEE[1], B. VERMILLION[1], D. KAMPER[2];
[1]Biomed. Engin., Catholic Univ. of America, Biomed. Eng., Washington, DC; [2]Biomed. Engin., Illinois Inst. of Technol., Chicago, IL

Abstract: The problem of muscle redundancy arises in human movement production, as the central nervous system (CNS) needs to select particular muscle coordination patterns out of an infinite set of possible combinations (Bernstein, 1967). Coordination of the hand muscles, in particular, is a complex neuromechanical process due to the high number of degrees-of-freedom to be controlled, the large number of muscles involved, and the complex biomechanics of the multiarticular musculotendon units. While some studies indicated that certain dimensionality reduction processes are involved in the coordination of hand muscles (e.g., employing a smaller number of muscle modules, Overduin et al., 2008; scaling fixed coordination patterns across different fingertip force levels; Valero-Cuevas, 2000), others have demonstrated by analyzing the within-trial variability structure of muscle coordination that hand muscle activation patterns can be modulated in relation to task requirements (Kutch et al., 2008; Valero-Cuevas et al., 2009). This suggests that multi-muscle coordination can be modulated. In this study, we explored feasibility of a novel technique to provide peripheral sensation in order to modulate coordination of the hand muscles. Specifically, we provided targeted assistance to hand muscles by pulling

exotendons, whose geometry and kinetic function emulate those of targeted hand muscles (Lee et al., 2014), by electric motors. We then examined if muscle coordination is affected by peripheral sensory inputs induced by these exotendons. Six subjects participated in a pilot experiment in which they were instructed to produce isometric dorsal fingertip force equivalent to 50% of their maximum voluntary force. Activities of three task-related muscles, extensor digitorum communis (EDC; agonist), flexor digitorum superficialis (FDS; antagonist), and first dorsal interosseous (FDI; synergist) were recorded during force production while two types of external assistance conditions were applied: 1) EDC assistance; and 2) FDI assistance. Targeted assistance of the EDC muscle primarily led to an increase in the activation of the antagonist of the targeted muscle (i.e., 27.6% increase in FDS activation) with a small decrease in both EDC and FDI activations during task performance. FDI assistance exclusively reduced the activation level of FDI, by over 40%. FDS activity increased to a much smaller extent (8.7% increase in FDS activation). The outcomes of this study indicate that coordination of hand muscles performed by CNS is affected (and can be modulated) by peripheral sensory inputs (e.g., internal normal/shear forces in finger joints) produced by exotendons.

Disclosures: S. Lee: None. **B. Vermillion:** None. **D. Kamper:** None.

Poster

803. Finger and Grasp Behavior and Kinematics

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Title: Distinct influence of hand posture on cortical activity during human grasping

Authors: *M. A. PEREZ[1,2], J. C. ROTHWELL[3];
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Abstract: We recently showed that subcortical circuits contribute to control the gain of motor cortical inputs to spinal motoneurons during precision grip of a small object. Here, we examine whether the involvement of the motor cortex could be revealed by grasping with different hand postures. Using noninvasive cortical, cervicomedullary, and peripheral nerve stimulation we examined in humans motor-evoked potentials (MEPs) and the activity in intracortical circuits (suppression of voluntary electromyography) and spinal motoneurons (F-waves) in intrinsic hand muscles when grasping a 6 mm cylinder with the index finger and thumb while the hand was held in the neutral position or during full pronation and supination. We demonstrate that the size of cortically evoked MEPs in the first dorsal interosseous, but not in the abductor pollicis brevis and abductor digit minimi muscles, was reduced to a similar extent during grasping with the hand pronated or supinated compared with the neutral position. Notably, the suppression of MEPs was present from the MEP onset, suggesting that indirect corticospinal pathways were less likely to be involved than direct connections. There was less intracortical inhibition targeting the first dorsal interosseous during hand pronation and supination compared with neutral and this negatively correlated with changes in MEP size. In contrast, cervicomedullary MEPs and F-waves remained unchanged across conditions, as did MEPs evoked during unopposed weak flexion of the index finger. Our findings reveal a distinct influence of the posture of the hand on the activity of cortical pathways controlling different hand muscles during grasping.

Disclosures: M.A. Perez: None. **J.C. Rothwell:** None.

Poster

803. Finger and Grasp Behavior and Kinematics

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Craig H. Neilsen Foundation Grant 261299

Title: Cortical contribution to different types of grip in intact humans

Authors: *T. TAZOE, M. A. PEREZ;
Dept. of Neurolog. Surgery, The Miami Project to Cure Paralysis, Univ. of Miami, Miami, FL

Abstract: The corticospinal system largely contributes to the control of hand function. However, evidence also supports the view that other systems are involved in the control of hand muscles. For example, studies in non-human primates demonstrated that cortico-motoneuronal cells fired more strongly during precision grip even though activity in the muscle tested was stronger for the power grip. Using transcranial magnetic stimulation over the hand motor cortex we examined motor evoked potentials (MEPs) and intracortical inhibition (suppression of voluntary electromyography, svEMG) in the first dorsal interosseous (FDI) muscle during isometric index finger abduction (control task), precision grip of a small cylinder between the index finger and thumb, and a power grip at matched levels of background electromyographic activity in the FDI muscle. We found that FDI MEP size decreases during precision grip (by 21.9±4.2%) and power grip (by 41.3±5.4%) compared with index finger abduction. Notably, the majority of subjects showed a similar MEP onset latency during index finger abduction and precision grip, whereas the MEP onset latency during power grip was delayed compared with index finger abduction (n=15/18, 0.58±0.11 ms) and precision grip (n=13/18, 0.64±0.14 ms), suggesting that other inputs are involved. svEMG decreased during precision grip by 25.8±11.4% and during power grip by 56.3±8.3%. A correlation was found between changes in svEMG and MEP size across conditions. Our findings indicate that precision and power grip exert a different influence on cortical circuits controlling the FDI muscle and support the view that power grip involves different neural sources than precision grip.

Disclosures: T. Tazoe: None. **M.A. Perez:** None.

Poster

803. Finger and Grasp Behavior and Kinematics

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Topic: D.17. Voluntary Movements

Title: Grip force responses after sudden and unpredictable increase in load force: The effect of load force direction

Authors: *K. C. LIMA, R. V. PEREIRA, P. B. DE FREITAS;
Univ. Cruzeiro Do Sul, São Paulo, Brazil

Abstract: Rapid grip force (GF) adjustments are needed to avert object slippage after unexpected increase in tangential load force (LF). Previous studies showed that when LF unexpectedly increased the central nervous system (CNS) used afferent information mainly from skin mechanoreceptors (i.e., FAI receptors) to trigger GF responses. Also, studies showed that when LF increased towards gravity, as an object tends to move downward, GF response initiated earlier than when LF increased against gravity and that the amount of GF applied just after the perturbation was based on the rate of LF change, which depends on the magnitude of perturbation. However, it is unknown if there would be a linear relationship between the amount of GF exerted and the magnitude of perturbation and if it is direction-dependent. Thus, the aims of the study were to investigate the effect of LF direction on GF response initiation (GFonset) and examine the effect of LF direction on the relationship between the magnitude of perturbation and the GF response. Eleven healthy and right-handed young adults were firstly asked to hold an instrumented object (m=132g) during 12 s, using the thumb and index finger of their right hand. The GF mean was calculated during this trial and used to determine the maximum and minimum values of GF allowed in the holding phase before perturbation (±50% of GF mean). Next, this object was suspended and kept stable by nylon threads fixed on the top and on the bottom of this object and by weights (367g each) fixed on the opposite extremities of these threads. The weights were linked to the threads by two electromagnets controlled by the experimenter. In this second condition, participants were asked to hold the object for 16 s and were warned that at any time the object could move either upward or downward, or stay at the same place. They were instructed to keep the object stationary after the perturbation. The GFonset, GF peak (GFpk), and acceleration peak (Apk), which determines the magnitude of perturbation, were calculated. No effect of direction was found for Apk. The GFonset was lower when the LF increased downward than when it increased upward (128.1±8.9 and 169.8±20.5ms, respectively). Moreover, while we found a strong positive correlation between GFpk and Apk for LF increasing in downward direction (r=0.87), no correlation was found for LF increasing in upward direction. These findings (low GFonset and strong GFpk and Apk correlation) indicate that the CNS is set to respond to perturbations towards gravity (default response) and when perturbation is not to this direction the CNS takes more time to respond (high GFonset) and do not adjust the amount of GF to the magnitude of the perturbation.

Disclosures: **K.C. Lima:** None. **R.V. Pereira:** None. **P.B. de Freitas:** None.

Poster

803. Finger and Grasp Behavior and Kinematics

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Topic: D.17. Voluntary Movements

Title: Assessment of force coordination and neuromuscular quickness through an object manipulation task

Authors: *M. UYGUR[1], K. HABERLAND[2];
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Abstract: Hand function and neuromuscular quickness are two of the most important aspects of motor function that could be seriously affected by aging and neurological diseases. Deteriorations in these functions could increase the risk of falling and decrease the quality of life of an individual. Therefore, the assessment of these motor functions has crucial importance in clinical and rehabilitative settings. Hand function has been quantitatively evaluated through the coordination between grip force (GF; the perpendicular force) and load force (LF; tangential forces that overcomes the weight and inertia) during object manipulation tasks. Neuromuscular quickness, on the other hand, has been assessed through isometric force production tasks completed under instructions to produce quick force pulses to varying submaximal amplitudes. It has been shown that a positive, linear relationship exists between the peak value of the force pulse produced and the peak value of the corresponding rate of force development. The slope of this relationship is named as rate of force development scaling factor (RFD-SF), which is used as an index for neuromuscular quickness. The aim of our study is to develop a simple technique that assesses force coordination and neuromuscular quickness simultaneously and to test the effects of force production direction on these assessments. We hypothesized that the indices of force coordination (GF/LF ratio, cross correlation between GF and LF and the corresponding time lags) in brief force production tasks will be high and those indices will be similar between pulses completed in upward or downward directions. We also hypothesized that the RFD-SF obtained from GF and LF would be similar and that the force direction would not affect this relationship. Six male and six female healthy young adults were asked to hold an externally fixed GF-LF measuring device and to produce submaximal isometric force pulses by pulling up or pushing down on it. Results revealed high and similar indices of force coordination between pulses produced in each direction implying elaborate force coordination in both directions. Regarding the quickness indices of GF and LF, results revealed a higher RFD-SF of LF than of GF in both force directions indicating a quicker LF production than GF production. Results also indicated that there was no effect of force direction on RFD-SF obtained from either GF or LF, individually. Overall, these findings suggest that brief force production tasks should be further evaluated as clinical tests of hand function and neuromuscular quickness in various populations.

Disclosures: **M. Uygur:** A. Employment/Salary (full or part-time):; Rowan University. **K. Haberland:** None.

Poster

803. Finger and Grasp Behavior and Kinematics

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Topic: D.17. Voluntary Movements

Support: NSF Grant BCS-1153034

Title: Dexterous manipulation: Learning interference induces increase in effort

Authors: ***Q. FU**, M. SANTELLO;
Arizona State Univ., Tempe, AZ

Abstract: Previous studies have shown that learning of a multi-digit manipulation task induces interference on the learning of a subsequent manipulation task requiring opposite actions of the hand. Additionally, a given manipulation task can be performed with different combinations of digit forces due to biomechanical redundancy. However, little data exist about the adaptation of digit forces through learning of manipulation, and how such adaptation could be affected by motor interference. We addressed these questions through a novel experimental design based on velocity-dependent torque perturbations delivered by haptic devices. Subjects (n=6) were asked to grasp a sensorized grip handle by positioning their thumb, index, and middle finger on force/torque sensors and lifted the handle up to a target zone within 450-550 ms while preventing the rotation of the handle. Two haptic robots were connected to the left and right side of a grip handle to generate the perturbations in the opposite directions for manipulation contexts A and B. The experimental sequence started with 41 Baseline trials (no torque), followed by 66 A-trials then 58 B-trials on the same day. Subjects performed another 41 B-trials followed by 58 A-trials on the following day (i.e., A1B1B2A2). We found that learning in B1 was slower than in A1 on the first day, indicating that learning interference occurred. By measuring digit forces, we also found that subjects used more effort in the beginning of the block and gradually reduced the effort in both A1 and B1. Importantly, the initial increase of effort was greater in B1 than in A1. When subjects were tested on the second day with B2, they showed faster re-learning and no change in effort. Interestingly, subjects increased their effort when switching back to A2 significantly more than the initial increase in both A1 and B1, although the learning rate was the same as A1. This indicates that the increase in effort was not dependent on the actual error. Overall, our results suggest that learning interference at the switch of manipulation contexts

induces temporary increase in effort. The extent to which this effort increases may depend on the number of repetitions with manipulations during the pre-switch context.

Disclosures: Q. Fu: None. **M. Santello:** None.

Poster

803. Finger and Grasp Behavior and Kinematics

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Topic: D.17. Voluntary Movements

Support: NICHD

NINDS

Burroughs Wellcome Fund

Title: Monkeys can use continuous haptic feedback to stabilize an unstable cursor

Authors: *K. M. QUICK[1,2], J. MISCHEL[1,2], P. LOUGHLIN[1], A. BATISTA[1,2];
[1]Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA; [2]Ctr. for the Neural Basis of Cognition, Pittsburgh, PA

Abstract: Natural movements are typically guided by sensory feedback. To better understand the complex links between sensation and motor control, we developed a novel paradigm, the Critical Stability Task (CST), to study sensory feedback's role in motor control in primate neurophysiology studies. During the CST, monkeys made serial hand movements to keep a cursor centered on a target. In the absence of these hand movements, the cursor's unstable dynamics caused the cursor to drift from the target at an increasing velocity. The monkeys received either visual feedback or haptic feedback about the cursor position. During visual feedback, if the monkey saw the cursor drift right, the monkey tried to stabilize the cursor by moving its hand to the opposite position on the left, and vice versa. During haptic feedback, the monkey instead experienced the cursor position via two vibrating motors placed on the non-reaching arm. The difficulty of the CST was manipulated by changing the cursor's instability level across trials; a higher instability level caused the cursor to move faster, necessitating faster and more precise corrective movements to stabilize the cursor. A trial was successful if the monkey stabilized the cursor for 6 seconds. We determined the maximal instability level that monkeys could successfully stabilize for half the trials. This allowed a direct comparison of visual and haptic feedback performance. Our main finding is that monkeys can learn to use an

artificial sensory stimulus to shape a long-duration, continuous movement that stabilizes an instability. After several months, two monkeys could use haptic feedback to stabilize 2/3 of the maximum instability level that they stabilized using visual feedback. We also measured the sensorimotor lag between the feedback signals and the corresponding hand movements. We found that the sensorimotor lag was larger during haptic feedback than during visual feedback. This may in part explain the decreased performance during haptic feedback versus visual feedback. Interestingly, we also found that the sensorimotor lag could change with the degree of task difficulty: rather than applying their fastest achievable sensorimotor lag at all instability levels, monkeys used a longer sensorimotor lag at the easier, lower instability levels. The CST can complement classic point-to-point reaching paradigms in several ways: first, it will allow us to probe the neurophysiological mechanisms of continuous, feedback-driven movements. Second, it provides a way to quantitatively compare the effectiveness of different sensory feedback modalities. This will be important in the development of bidirectional brain-computer interfaces.

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Poster

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Program#/Poster#: 803.17/T11

Topic: D.17. Voluntary Movements

Title: Anthropometry of passive wrist stiffness

Authors: ***S. K. CHARLES**[1], S. D. GRIMSHAW[2], D. B. SEEGMILLER[3], A. L. PANDO[3], N. HOGAN[4], H. LEE[5,6];
[1]Mech. Eng. and Neurosci., [2]Statistics, [3]Mechanical Engin., Brigham Young Univ., Provo, UT; [4]Mechanical Engin. and Brain and Cognitive Sci., MIT, Cambridge, MA; [5]Sensory Motor Performance Program, Rehabil. Inst. of Technol., Chicago, IL; [6]Sch. for Engin. of Matter, Transport, and Energy, Arizona State Univ., Tempe, AZ

Abstract: While decades of motor neuroscience studies have investigated how the neuromuscular system controls the inertial dynamics of shoulder and elbow (reaching) movements, recent studies have shown that the dynamics of distal joints (forearm, wrist, and fingers) are dominated by stiffness, not inertia. However, we do not know how joint stiffness varies between individuals, so it is not currently possible to accurately estimate an unimpaired individual's joint stiffness or to compare an impaired individual's stiffness to normative data to

determine the degree of impairment. The long-term goal of this study is to develop anthropometric regression equations to estimate individuals' passive wrist stiffness from easily measured characteristics. Here we present preliminary data from the initial cohort of subjects. Thirty-two young, healthy subjects participated in this study. Subjects' forearm and hand were attached to a rehabilitation robot (Interactive Motion Technologies, Watertown, MA) that slowly rotated the wrist in combinations of flexion-extension and radial-ulnar deviation. Subjects were instructed to relax as much as possible, and EMG measurements were used to exclude any measurements in which subjects were not sufficiently relaxed. Subjects' 2-by-2 stiffness matrices were calculated from recorded torque-displacement data by multiple linear regression. We computed for each stiffness matrix the area, anisotropy, and orientation of the associated stiffness ellipse, and regressed these ellipse parameters against subject characteristics (age, gender, BMI, height, hand and forearm lengths and circumferences, maximum voluntary torque, and movement direction). Since the height, lengths, circumferences, and torques are known to be highly collinear, we grouped them into a single latent variable termed "stature" determined by principal components analysis. Previous qualitative observations indicated that the area of the stiffness ellipse, which likely depends on muscle cross-sectional area, increases with body size, whereas the anisotropy and orientation, which reflect musculoskeletal geometry, are relatively stereotyped between subjects. We found that the latent variable stature, which represents body size, did have a significant effect on area ($p = 0.024$), but unexpectedly also on anisotropy ($p = 0.047$). We are currently working to increase the size and diversity of the subject population, but these preliminary results indicate that wrist joint stiffness varies in a predictable manner and can therefore be estimated from easily measured subject characteristics.

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Poster

803. Finger and Grasp Behavior and Kinematics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 803.18/T12

Topic: D.17. Voluntary Movements

Support: FWO Odysseus, Belgium

BBSRC David Phillips fellowship, UK

Title: Sensorimotor memory biases weight perception in a grip-lift task

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Abstract: When lifting a series of objects, the previous lift influences the planning of fingertip forces for the next lift. For instance, grip force rates are higher after a heavy object has just been picked up compared to a light one. This effect is called sensorimotor memory. Here we investigated whether the order of lifting also affects perception of object weight. Twenty subjects were asked to grip and lift equally sized but differently weighted objects in a semi-randomized order. When the previous trial was a heavy object, peak grip and load force rates were higher and loading phases were shorter than when a light object was previously lifted. This sensorimotor memory effect was found during lifts of both light and heavy objects. Interestingly, weight estimation of an object was significantly lower when preceded by a heavy object compared to a light. This finding suggests that feedback mechanisms involved in force control influence perception of weight and a sense of effort might actually be perceived. A control experiment in which forces were passively exerted on a resting hand showed no perceptual biases due to presentation order. Moreover, the size of the sensorimotor memory effect correlated with the amount of perceptual bias in the grip-lift task, indicating that a larger sensorimotor memory effect was associated with a larger difference in weight estimation. These results were only seen for light objects. The absence of an effect for heavy objects might be explained by the Weber law and possible feedback corrective mechanisms that occur during the longer loading phase for heavy objects. Together, these results suggest that the control of grip force and perception of weight are linked.

Disclosures: V. Van Polanen: None. **M. Davare:** None.

Poster

803. Finger and Grasp Behavior and Kinematics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 803.19/T13

Topic: D.17. Voluntary Movements

Title: Maturation of grip force control in older children and adolescents

Authors: W. SCHERMER, M. CAMINITA, *S. H. BROWN;
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Abstract: Developmentally, studies have indicated that control of grip force matures by mid to late childhood (Blank and Hermsdorfer, 2009; Blank et al., 2000; Deutsch and Newell, 2001). In contrast, others have shown continued maturation into early adulthood, particularly in the control of high submaximal forces (Halder et al., 2007). Most studies examining the maturation of grip force have focused on submaximal forces which are typically higher than those required for many daily activities (Rice et al., 1998). Further, it is unclear whether maturation of grip force control is affected by the direction of force modulation (i.e. increasing or decreasing force). The purpose of this study was to examine the development of targeted force control as a function of submaximal force magnitude and direction in older children and adolescents. Typically developing, right-handed males were assigned to one of two age groups: 8-12y and 16-20y. Using hand-held dynamometers, participants produced visually-guided grip forces in response to a step change in a computer-displayed target force level. Tasks were performed with the dominant and non-dominant hand and varied in difficulty using two submaximal target forces (5%, 20% maximum voluntary contraction) and by altering the need to maintain a specific force level prior to and following a step change in target force. Once the force level was established, participants maintained a static target force for 4 sec. Dependent variables were time to reach the force target, rate of force change, and variability during force maintenance. Grip force control improved with age as seen by more rapid changes in force modulation and a reduction in static force variability in the adolescent group ($p<.01$). Regardless of age, static force variability was significantly greater at 5% compared to 20% MVC ($p<.01$). Older children took longer to modulate force regardless of force direction ($p<.01$). In both age groups, the need to control force prior to and at target acquisition did not affect force control. No differences were observed between hands across all tasks despite hand differences using functional measures of hand dexterity ($p<.05$). These results indicate that grip force control continues to mature into late adolescence with the generation of low submaximal forces providing a greater control challenge regardless of age. To what extent these findings reflect age-related differences in sensory processing of force-related sensory feedback and/or predictive force control strategies requires further investigation. **1924/2300**

Disclosures: W. Schermer: None. **M. Caminita:** None. **S.H. Brown:** None.

Poster

803. Finger and Grasp Behavior and Kinematics

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 803.20/T14

Topic: D.17. Voluntary Movements

Title: Finger tapping ability in the dominant and non-dominant hands

Authors: *T. AOKI;
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Abstract: The abilities of individual fingers during the performance of fast, repetitive tapping movements were compared between the dominant and non-dominant hands in ten healthy young males and females. All subjects were right-handed, as determined by the Edinburgh MRC Handedness Inventory (Oldfield 1971). The subjects completed two tasks. The first task (single-finger tapping) was to tap a force transducer for 7 sec as fast as possible using only one finger (the index, middle, ring and little fingers), while the another task (double-finger tapping) was to complete the same activity but tapping with two fingers alternately (the index-middle, middle-ring, and ring-little finger pairs). All conditions were performed by the dominant right and non-dominant left hands. The order of the tasks was randomized, and within each task the order of finger or finger pair was also randomized. In all tasks, the subjects were instructed to keep their "resting" (non-tapping) fingers in contact with the transducers. Tapping and non-tapping finger forces were measured using four force transducers. In the single-finger tapping, inter-tap intervals with the dominant hand were significantly shorter than the non-dominant hand in all fingers. Parallel changes were observed in the key-contact force of the non-tapping fingers during tapping. The sum of average forces over the entire 10-tap period for the three non-tapping fingers was significantly larger for the dominant hand in all fingers than the non-dominant hand. On the other hand, there was no significant difference between the dominant and non-dominant hands in all fingers for sum of the ranges of forces for the three non-tapping fingers. In the double-finger tapping, inter-tap intervals with the dominant hand were significantly shorter than the non-dominant hand in the index-middle and middle-ring finger pairs. Interestingly, significant difference between the dominant and non-dominant hands was not observed in the ring-little finger pair. Observed superior finger tapping abilities in the dominant hand in most of all conditions for right-handed adults can be due to effect of daily use on the development at the central nervous system. Similar finger tapping abilities between the dominant and non-dominant hands in the ring-little fingers may be attributed to less frequent combined use of the ring and little fingers for both of the dominant and non-dominant hands in daily activity.

Disclosures: **T. Aoki:** None.

Poster

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Support: NSF Grant EEC1156916

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Title: Effects of goal-directed mirror visual feedback on cortical excitability in the untrained hemisphere

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Abstract: In persons with hemiplegia due to stroke, mirror visual feedback (MVF) of movements performed with the unaffected limb, can recruit brain areas controlling the stroke-affected limb and aid recovery. Given evidence that goal-directed, relative to goal-free movements, elicit stronger bilateral activation, we ask here if goal-directed mirror training may likewise elicit stronger activation in the untrained (ipsilateral) M1. Following informed consent, 10 healthy subjects performed 4 blocks (B1-B4) of index-finger flexion movements using their dominant right hand, with feedback presented in a virtual environment. Each subject completed 4 protocols, randomly ordered: veridical feedback with (VG) and without (VF) a goal, and MVF with (MG) and without (MF) a goal. In the goal protocol (MG, VG), subjects moved to 3 targets (20º, 40º, 60º). In the no-goal protocol (MF, VF), subjects performed non-targeted flexion movements. Transcranial magnetic stimulation was used to elicit motor evoked potentials (MEPs) in the left first dorsal interosseous (FDI) and abductor digiti minimi (ADM) muscles prior to training and after each block to track cortical excitability in the untrained M1. Targeted movement kinematics without visual feedback were measured before and after training to assay learning. Separate rmANOVAs were used to analyze MEP amplitudes [Feedback (MG, MF, VG, VF), Block (Pre, B1-4)], and absolute angular error [Feedback (MG, MF, VG, VF), Time (Pre, Post) and Hand (Left, Right)]. For MEPs of the untrained FDI a significant ($p<.05$) main effect of Time, and a significant Time x Feedback interaction was noted. Post-hoc testing confirmed that the MEPs significantly increased relative to PRE in B3 (178%) and B4 (175%) for the MG condition only. No significant changes in MEPs were noted for the uninvolved ADM, suggesting a task-specific effect. Analysis of kinematics revealed no significant effects suggesting M1 excitability changes may reflect priming, rather than an interhemispheric transfer of information. To test the intra and interhemispheric drivers of M1 excitability in the MG condition, 5 subjects were tested using paired-pulse TMS-based measures of short intracortical inhibition (SICI), intracortical facilitation (ICF), and interhemispheric inhibition (IHI). Trends indicating decreased SICI and IHI were noted in the preliminary dataset. Our data suggest that performing goal-directed movements during MVF imparts the most robust M1 activation, and that this activation

is 1) task specific (e.g. muscle-specific), 2) may reflect a priming rather than an information-transfer effect, and 3) possibly mediated by SICI- and IHI-based mechanisms.

Disclosures: T. Manuweera: None. **M. Yarossi:** None. **S. Adamovich:** None. **E. Tunik:** None.

Poster

803. Finger and Grasp Behavior and Kinematics

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Topic: D.17. Voluntary Movements

Support: AHA Fellowship 13PRE14610017

NIH Grant 1R21HD055478-01

Title: Involuntary finger-thumb coupling during a pinching task

Authors: *D. G. KAMPER[1], C. L. JONES[2];
[1]Biomed Engin., Illinois Inst. Technol., Chicago, IL; [2]Biomed. Engin., Illinois Inst. Technol., Chicago, IL

Abstract: Highly individuated movement of the digits, especially for the index finger and thumb, is one of the hallmarks of human motor control. While great independence of movement is possible, tightly coordinated activity among the digits is required to achieve many activities of daily living. For example, the thumb tip and fingertip forces must balance each other when pinching an object, but both must also respond to perturbations to the object or its surface. As this coordination is incompletely understood, we ran a set of experiments to explore the coupling between the thumb and index finger during pinching movements. Accordingly, a cable-actuated finger exoskeleton (CAFE) was created to provide precise, strong, high-bandwidth perturbations to the index finger during dynamic movement. The CAFE is capable of independently actuating each joint of the index finger under force or position control. Neurologically intact participants were instructed to move their index finger and thumb from an extended posture with the hand open through a palmar pinching motion until fingertip and thumb tip made contact, and then back to the starting posture. Electromyographic signals were recorded with a combination of surface and intramuscular electrodes for 5 different muscles in the index finger and thumb. Kinematics for the thumb were recorded with an optical tracking system. The CAFE was employed to provide two types of perturbations to the index finger during either the opening or

closing phase of these movements. In the first group of experiments, the CAFE randomly rotated the MCP joint 40° into either flexion or extension at 600°/s during the pinching movement on selected trials. A total of 10 trials were performed for each of the four conditions: flexion/extension, closing/opening. An additional 20 trials were conducted where no perturbation was delivered. In the other group of trials, impedance of either the metacarpophalangeal (MCP) joint or distal and peripheral interphalangeal (IP) joints was suddenly increased to restrict further movement during either the opening or closing phase. Ten trials were conducted at each of the four conditions: MCP/IP, closing/opening, and twenty trials with no perturbation were randomly interspersed. Imposed displacement of MCP in the first set of trials produced stretch reflex activity in the perturbed finger muscles, but also a heteronymous reflex response in the non-stretched muscles of the thumb. Similarly, the sudden increase in joint impedance in the index finger led to reduced movement of the unperturbed thumb. In both cases, the degree of finger-thumb coupling varied with phase of movement.

Disclosures: D.G. Kamper: None. **C.L. Jones:** None.

Poster

803. Finger and Grasp Behavior and Kinematics

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Topic: D.17. Voluntary Movements

Support: NS-035032

AR-048563

Title: Synergy in a space of control variables during a finger force production task

Authors: *S. AMBIKE[1], D. MATTOS[2], V. ZATSIORSKY[1], M. L. LATASH[1];
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Abstract: We used the framework of the referent configuration hypothesis to explore the possibility that accurate performance can result from inter-trial co-variation among control variables that show relatively high variability. In particular, we assumed that force production by a finger in isometric conditions results from controlling the fingertip referent coordinate (R) and apparent stiffness (C) and is governed by the equation: force = R × C. Therefore, a hyperbolic function in the {R, C} space defines the solution space for the task of producing a certain force

(the uncontrolled manifold, UCM, for that task). We explored whether inter-trial variability in {R, C} was organized to keep deviations from the UCM low while allowing large deviations within the UCM. Subjects produced a specified constant force (25% of maximal voluntary contraction force) with a finger or all four fingers together by pressing downward on force sensor(s). Visual feedback on the instructed force was provided for the first 5 s and then removed while the subjects were instructed to keep performing the same action. Next, all fingers and sensors were gently raised (1 cm over 0.5 s), starting at an arbitrary time within a 2-s window, leading to an increase in the force. Subjects were instructed and trained to 'not interfere' with the external perturbation. Linear regression in the force-coordinate plane was used to estimate the apparent stiffness C and the intercept, which provided an estimate of R (referent position corresponding to zero force). R and C values computed across multiple trials displayed a hyperbolic distribution with consistently high R^2 values (> 0.9) for all task conditions and subjects. Further, we created a surrogate data set by shuffling the R and C values measured in different trials and re-computing the force (= R × C). Force production accuracy in the surrogate data sets was consistently smaller than in the actual sets confirming that the inter-trial co-variation in the {R, C} space was used to achieve accurate performance despite large variation in both R and C. Our results provide support for the referent configuration hypothesis and its more classical version - the equilibrium-point hypothesis. Note that R and C are produced by physiological control signals (thresholds of the tonic stretch reflex, λs) to the involved muscles, which are expected to covary to stabilize {R, C} to within their observed ranges. To our knowledge, this is the first experimental demonstration of hierarchical control expressed in terms of the fundamental control variables, such as {R, C}, and is an important step towards the analysis of synergies in the λ-space.

Disclosures: **S. Ambike:** None. **D. Mattos:** None. **V. Zatsiorsky:** None. **M.L. Latash:** None.

Poster

804. Finger and Grasp Mechanisms

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Topic: D.17. Voluntary Movements

Title: Proximal and distal coding of sensorimotor parameters in the control of arm movements

Authors: K. REGNERY[1], N. NATRAJ[2], K. OH[2], B. PRILUTSKY[2], L. WHEATON[2], *J. C. MIZELLE[2];
[1]Georgia Inst. of Technol., Atlanta, GA; [2]Sch. Applied Physiol, Georgia Tech., Atlanta, GA

Abstract: Sensory feedback from the principal modalities (e.g., vision and somatosensation) are critical in the internal model framework, for estimation of the current state of the sensorimotor system, predicting future sensorimotor states given some motor command, and also for the on-line control of movement. The precise nature of how sensory feedback is used in coding the sensorimotor state has not yet been fully identified. More specifically, we sought to answer whether the sensorimotor state was estimated by the relative position of the end effector, or whether this estimation relied on the relative joint positions of the more proximal segments. As such, we designed an experiment where participants deprived of visual feedback performed a limb mirror-matching task with and without reduced sensory feedback from the end effector. A planar robotic apparatus moved the left arm from a constant starting postural configuration into one of four new postural configurations. Participants then actively moved the right arm to mirror this new postural configuration such that the elbow and shoulder joint angles of the right arm were equal of those of the left. In the first half of the experiment, participants had normal sensory feedback from the end effector of the left arm. For the second half of the experiment, we used ischemic deafferentation to reduce sensory feedback from the end effector (hand) of the left arm by inflating a blood pressure cuff placed on the distal forearm. Elbow and shoulder joint kinematics and the position of the middle fingertip were recorded for each experimental trial. Given the one-to-one mapping between finger position and the elbow and shoulder angles, virtual targets related to the expected fingertip location for each of the four postural configurations were also created, and errors between the actual fingertip position and these virtual targets were calculated. We observed similar elbow and shoulder kinematics regardless of deafferentation, but greater errors in finger location with reduced end effector sensory feedback. Thus, our results suggest a dual processing strategy, wherein proximal sensory feedback is sufficient to guide the finger to an approximate spatial location, and then sensory feedback from the end effector refines the spatial estimate. This study highlights the importance of sensory feedback from the end effector in sensorimotor state estimation for motor control and has implications for clinical populations suffering from reduced afferent sensory information.

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Poster

804. Finger and Grasp Mechanisms

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Topic: D.17. Voluntary Movements

Support: Grants-in-Aid for Scientific Research Grants-in-Aid for Scientific Research Grants-in-Aid for Scientific Research (C) 25351000

Title: Cortical EEG oscillations can predict the variability of MEP amplitudes

Authors: *K. OGATA[1], H. NAKAZONO[2], S. TOBIMATSU[2];
[1]Grad Sch. Med. Sci, Kyushu Univ., Fukuoka, Japan; [2]Kyushu university, Fukuoka, Japan

Abstract: [Objective] Motor evoked potentials (MEPs) are obtained by transcranial magnetic stimulation (TMS) over the primary motor cortex (M1), but their amplitudes often vary stimulus by stimulus. We hypothesized that EEG oscillations just before TMS could predict MEP amplitudes. Thus, we evaluated the relationship between EEG oscillations and MEP amplitudes to determine the underlying mechanism of the variability of MEP amplitudes. [Methods] Twelve healthy adults were recruited in Experiment 1. EEGs were obtained at 19 locations (international 10-20 system), and EMGs were recorded from right FDI. Left M1 hotspot was stimulated by TMS with the intensity to obtain about 1 mV MEP amplitudes. Interstimulus interval was set at 5 - 7 s. MEPs and EEGs were recorded for 200 times in total for each subject under eyes-open (EO) and eyes-close (EC) conditions. EEGs were segmented between -500 and 0 ms of TMS onset, and the power values were calculated by wavelet analysis. EEG powers of 8 - 30 Hz were compared between the epochs of high and low amplitude MEPs. In Experiment 2, the influence of low TMS intensity was evaluated under EO condition. EEGs from 8 subjects were compared between the two conditions of different TMS intensities; high TMS intensity was set to elicit 1 mV MEPs as in Experiment 1 and low intensity was fixed at resting motor threshold. [Results] EEG powers of α and β range were enhanced at C3 when MEP amplitudes were larger in both EO and EC conditions (Experiment 1). When the EEG power difference of high/low MEPs was compared between EO and EC conditions, the power differences in α and low β range under EO was more increased than that of EC at frontal and parietal leads. On the contrary, EEG powers were reduced at C3 when MEP amplitudes were larger in the low TMS condition (Experiment 2). [Discussion] Our results (Experiment 1) demonstrated that the larger α and β powers at C3 could predict the larger MEP amplitudes in both EO/EC conditions. Modulation of visual cortices by EO/EC probably influences distant cortical functions including M1 in relation to vigilance, attention or anticipation. Decreased EEG powers for larger MEP amplitudes with low TMS intensity (Experiment 2) were in accord with previous studies, in which decreased EEG powers were considered to reflect only local M1 excitability. How do we interpret paradoxical results of Experiments 1 and 2? The higher TMS intensity becomes, the more activated areas involve. Therefore, we speculate that the enhanced inputs from surrounding areas to M1 induced by high TMS intensity produce the larger MEP amplitudes.

Disclosures: K. Ogata: None. **H. Nakazono:** None. **S. Tobimatsu:** None.

Poster

804. Finger and Grasp Mechanisms

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Topic: D.17. Voluntary Movements

Support: Indonesian Endowment Fund for Education

Title: Movement intermittency: visuomotor feedback loop or intrinsic rhythmicity?

Authors: *D. SUSILARADEYA, F. GÁLAN, K. ALTER, A. JACKSON;
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Abstract: In tracking slow targets, humans are known to make periodic intermittent movement with a predominant frequency of 2 Hz, ranging from 1-4 Hz.[1] However, the mechanisms of this low-frequency rhythmicity in behaviour are not fully understood. Previously movement intermittency has been thought to be determined by sensorimotor loop delays, since artificially increasing these delays reduces the frequency of submovements. However, recent work has revealed an intrinsic rhythmicity within motor cortical networks at submovement frequencies around 3 Hz, including during sleep.[2] Therefore we re-examined the possibility of an intrinsic rhythmicity contributing to movement kinematics. First, we developed a novel 2D bimanual finger force tracking task with a target that followed circular trajectories with frequencies of 0.1 and 0.2 Hz. We observed a sharp peak in the power spectrum of the cursor speed at 2 Hz, irrespective of target speed or whether subjects made eye movements or fixated the centre of the screen. Tracking was associated with an increase in delta band (1-4 Hz) power in the electroencephalogram over sensorimotor cortex. This signal was coherent with cursor speed, at around 2 Hz. To investigate the role of visual feedback, we introduced delays of 100 ms, 200 ms, 300 ms and 400 ms. The main tracking frequency at 2 Hz shifted to a lower frequency as delay increased. Surprisingly, we observed a second higher frequency peak at twice the main frequency which became more prominent as delay increased. These data could be explained by a simple model in which intermittent movement commands arising from external visual feedback are filtered through motor circuits with intrinsic rhythmicity. We speculate that this intrinsic rhythmicity may help generate submovements with a kinematic profile appropriate for naturally-occurring feedback delays. References: 1. Vince MA. The intermittency of control movements and the psychological refractory period. Br J Psychol Gen Sect. 1948 Mar;38(Pt 3):149-57. 2. Hall TM, de Carvalho F, Jackson A. A common structure underlies low-frequency cortical dynamics in movement, sleep, and sedation. Neuron. Sep 3, 2014; 83(5): 1185-1199.

Disclosures: D. Susilaradeya: None. **F. Gálan:** None. **K. Alter:** None. **A. Jackson:** None.

Poster

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Title: Posterior parietal cortex informs self-action perception by integrating visual feedback about one's actions with internal movement-related cues from proprioception and forward models

Authors: M. J. ROTH[1,2], K. LAUER[1], M. SYNOFZIK[1], M. HIMMELBACH[1], *A. LINDNER[1];
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Abstract: Perception of one's own limb movements is not only informed by external (visual) information. It also relies on internal action-related information such as proprioception and efference copies of motor commands. An area that has access to these various types of information is posterior parietal cortex (PPC), rendering it an ideal neural substrate to inform self-action perception. In particular, it has been suggested that PPC represents forward models that enable predictions about sensory consequences of self-action based on efference copies. Such forward models are highly relevant for perception as they allow identifying sensory information that is self-produced. Moreover, they reliably inform perception about self-action without delays due to sensory processing and even in situations where external action-cues are unreliable or lacking. Here we tested the notion that PPC represents forward models for perception. To this end we contrasted performance between a group of 11 patients with lesions in PPC and a group of matched healthy controls: Subjects' task was to perform fast out-and-back pointing movements in a virtual reality setup, in which visual feedback about movements could be manipulated or omitted. Specifically, we acquired visual estimates of subjects' perceived pointing direction (i) in trials with veridical visual feedback, (ii) in trials with rotated visual feedback, and (iii) in trials without feedback. We also acquired visual self-action estimates in a passive pointing condition without feedback (iv) in which an experimenter was moving subjects' arms. Comparing this passive condition (iv) with the active case (iii) allowed us to infer the

respective contribution of forward models and proprioception on self-action estimates. Our experiments demonstrate that the reliability (the inverse of the variance) of self-action estimates significantly improved from passive to active pointing by a factor of roughly two, suggesting a contribution of both, proprioception and forward models to self-action perception. Interestingly, performance in both tasks (iii & iv) was indistinguishable between groups, questioning the notion of forward models for perception in PPC. Instead, in cases with rotated visual feedback (ii), patients self-action estimates relied to a significantly greater extend (about 1.7 times more) on that (manipulated) feedback as compared to controls. This suggests that the role of PPC in self-action perception is rather to integrate forward models and proprioception with visual information than to establish forward models in the first place. The latter might instead be a function of the cerebellum.

Disclosures: M.J. Roth: None. **K. Lauer:** None. **M. Synofzik:** None. **M. Himmelbach:** None. **A. Lindner:** None.

Poster

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Support: BBSRC David Phillips fellowship (UK)

FWO Odysseus (Belgium)

Title: Modulation of 5-30 Hz EMG-EMG coherence during grip force tasks with varying precision constraints

Authors: *R. TIBOLD[1], S. FARMER[1], M. DAVARE[1,2];
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Abstract: Skilled hand movements involve functional interactions across an extensive parieto-frontal cortical network. The neural mechanisms by which these structures cooperate spatio-temporally are not fully understood. One way to investigate how these different areas interact is to analyse common oscillatory drive in the electromyogram (EMG) since oscillatory activity facilitates synchrony between neuronal ensembles. Here we varied the task precision constraints

to test whether different levels of activity in sensorimotor loops could alter the oscillatory interactions between the neural sources that underlie grip force control. To address this issue we quantified changes in EMG-EMG coherence between rectified surface EMG signals acquired simultaneously from first dorsal interosseous and abductor pollicis brevis while healthy individuals (n=9) performed visuomotor grip force tracking tasks at distinct force levels requiring either low or high precision. In a "force control" condition, subjects squeezed with their index finger and thumb a manipulandum with 2 force sensors (ATI mini40-E) to move a cursor on a computer screen along a predefined force target path by controlling their force. In a "position control" condition, two Phantom Desktop (Geomagic) haptic devices were attached to the index finger and thumb. Subjects had to vary their grip aperture to move the cursor along the target path whilst force exerted by the robots was kept constant. We found tracking performance improved as precision constraints increased in the position but not force control task, suggesting sensorimotor feedback loops acted more efficiently when processing position rather than force. A pooled coherence analysis with extended Chi^2 statistics revealed (1) a significant increase in the magnitude of coherence at 9-11 Hz frequencies when comparing high vs. low precision conditions and (2) a suppression of the coherence at 16-30 Hz frequencies for both precision levels in the position control task. There was an overall lack of coherence changes in the force control task. We suggest the increased common drive in the alpha-band is a signature of an enhanced oscillatory activity in cortical ensembles involved in sensorimotor control of position, but not force signals. It is plausible alpha-band oscillations implement generic filtration of neural activity interfering with high precision requirements, thus reallocating the computational resources on the control of grasp. These results are in line with the disengagement theory of task-irrelevant cortical regions achieved through "gating by inhibition" where the necessary information is routed to the task-relevant brain areas.

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Poster

804. Finger and Grasp Mechanisms

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Topic: D.17. Voluntary Movements

Support: R00 HD073240

R01 NS053813

Title: Evidence for a transition in usage of cortical and subcortical structures during the learning process of human hand movement

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Abstract: A startling acoustic stimuli (SAS) causes the involuntary release of certain planned movements in humans referred to as startReact. This technique has been used as a probe of motor planning for many actions such as reaching or grasping; however, other actions like individual finger movements are not susceptible to startReact. StartReact is only intact when subcortical (e.g. reticulospinal) structures are utilized during execution. Researchers have theorized this reliance on subcortical pathways for initiation precludes finger movements from demonstrating an intact startReact (Carlsen *et al.,* 2009) because such movements are predominately mediated by cortical structures. But, recent work couched in non-human primate work has revealed reticulospinal involvement in such tasks (Soteropoulos *et al.,* 2012). Accordingly, the underlying reasoning behind finger movement's inability to startReact remains elusive. Alternatively, startReact susceptibility could relate to task familiarity. The task previously used to evaluate startReact in finger movements was index finger abduction – an uncommon task requiring a large cognitive (cortical) burden to accomplish. We hypothesized index finger abduction would be susceptible to startReact after repetitive task training, during which this task would become more familiar and require less cognitive burden. 10 healthy adults practiced index finger abduction over the course of a 10-day training regime. Trials consisted of "ready" and "go" commands. SAS was implemented between the two commands in roughly 20% of trials. Latencies between SAS and FDI (index finger abductor) EMG activation were recorded. Using EMG activation of the right and left sternocleidomastoid (SCM), SAS trials were further classified as startle present (SCM+) and startle absent (SCM-). A movement is considered susceptible to startReact when the FDI latency during SCM+ trials is faster than during SCM- trials. We found FDI latencies between SCM+ and SCM- trials were similar on day 1 (Δ = 2.9±12.6ms) but demonstrated faster SCM+ latencies (average = 92.6±10.1ms) compared to SCM- latencies (average = 101.0±11.1ms) by day 10 (Δ = 8.4±4.2ms). These data indicate index finger abduction is receptive to startReact after repetitive training. This susceptibility is accompanied by enhanced performance of the task; reaction times for voluntary trials (without SAS) decreased from day 1 to day 10 (Δ = 58.9±33.2ms). These results suggest that subcortical structures become increasingly important as a motor task is learned. In this way, startReact may be a useful probe not only of the allocation of neurological resources, but also of the learning process itself.

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Poster

804. Finger and Grasp Mechanisms

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 804.07/U4

Topic: D.17. Voluntary Movements

Support: ESRC

MRC

Title: The role of movement in metacognition: the relationship between movement speed and confidence

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Abstract: Previous studies have demonstrated that the confidence someone has in a decision they have made and whether or not that decision is correct are related. This is often referred to as metacognition. Furthermore, it is known that in such tasks participants' confidence ratings are correlated with the speed at which they reported their decision. Indeed, individuals can even estimate others' confidence levels from observing their movements while making a decision, with faster movements correlating with higher confidence. Currently, the mechanism by which we are able to correctly estimate our confidence in our decisions is not known. Recent work has shown that disruption of the motor system, specifically dorsal premotor cortex, significantly reduces metacognitive ability. This opens up the possibility that, at least in part, our confidence ratings of our own decisions are estimated from how we executed the action that indicated our decision. The link between cognition and action has been demonstrated in social psychology studies, where the adoption of high-power non-verbal displays (open, expansive postures) leads to increased reports of feelings of power and elevations in testosterone and reductions in cortisol, compared with subjects who adopted low-power displays (crossed limbs, contractive postures).

Here we tested the hypothesis that observation of our own movements modulates our estimate of our confidence in our decisions. 48 subjects (31 female, 17 male) with a mean age of 27 were recruited. Here we manipulated subjects' movement speeds using a movement priming task. They were then asked to make a binary decision on a perceptual contrast discrimination task, and indicate their response by moving an object to one of two containers. Subsequently, they reported their confidence in their decision using a numerical scale of 1-99, with 1 indicating minimum possible confidence, and 99 indicating maximum confidence. Preliminary analyses revealed that movement speed had a measurable effect on confidence. As expected, after the fast prime participants were quicker to indicate their decision and responded more slowly following the slow prime. For correct decisions there was no significant modulation in reported confidence ratings by the movement speed. However, for incorrect trials, as predicted, following the fast prime subjects significantly increased their confidence ratings compared to a decrease in confidence ratings subsequent to the slow prime. This finding suggests that humans obtain information about their confidence levels by monitoring their movement kinematics and that confidence can be manipulated by changing how subjects move.

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Poster

804. Finger and Grasp Mechanisms

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Topic: D.17. Voluntary Movements

Support: ERC parietalaction

BBSRC David Phillips fellowship (UK)

FWO Odysseus (Belgium)

Title: Interactions between different regions of ventral premotor cortex and contralateral M1

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Abstract: Recent brain imaging studies investigating the neural network underlying action observation suggest that sub-regions of the ventral premotor cortex (PMv) are functionally

different from one another. For instance, monkey area F5a responds to observing actions in a more general way, such as viewing the hand alone performing a grasp, mimicking actions and robot actions. In contrast, area F5c is only active when the observer views a whole person performing an action (Nelissen et al., 2005). Due to these functional differences, we hypothesised that the effective connectivity profile of different sub-regions within human PMv would also differ. Here, using paired-pulse transcranial magnetic stimulation (TMS), we examined the connectivity between two sub-regions of PMv and the contralateral primary motor cortex (M1) and compared it to interhemispheric inhibition (M1-M1), as a control for electrical current spread to M1. The two different PMv sites were the caudal part of the inferior frontal gyrus (IFGc, cortical surface MNI coordinates: X=55, Y=14, Z=29) as frequently used in previous studies (Buch et al., 2010, Davare et al., 2010) and the recently identified putative human homologue of F5c (phF5c, MNI coordinates from the fMRI: X=38, Y=0, Z=40; see Ferri et al., 2015). Whilst subjects (n=9) sat at rest, a single TMS pulse was given over the left M1 alone (test pulse) or after a conditioning pulse over right IFGc, phF5c or M1 at an inter-stimulus-interval (ISI) of either 8 or 10 ms. The conditioning stimulus was applied either at a subthreshold (80% of resting motor threshold; rMT) or suprathreshold (120% of rMT) intensity. Twenty motor evoked potentials (MEPs) were recorded from the first dorsal interosseous (FDI) for each condition (2 conditioning intensities x 2 ISIs x 3 sites x 20 = 240 MEPs in total). We found that a subthreshold conditioning pulse over right IFGc, phF5c or M1 had no effect on contralateral M1 MEPs at either ISI. Conversely, suprathreshold pulses over right IFGc, phF5c or M1 differentially modulated contralateral M1 MEPs, such that for both ISIs phF5c conditioned MEPs were significantly increased compared to IFGc and M1, whereas IFGc conditioned MEPs, and to a greater extent M1 conditioned MEPs, were significantly decreased compared to phF5c. Our results indicate that phF5c has a net facilitatory influence on contralateral M1 compared to the neighbouring IFGc, which shows a net inhibitory effect on M1, in line with previous studies. Altogether these two distinct effective connectivity profiles could highlight different mechanisms by which phF5c and IFGc influence M1 during action observation.

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Poster

804. Finger and Grasp Mechanisms

Location: Hall A

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Program#/Poster#: 804.09/U6

Topic: D.17. Voluntary Movements

Title: Quantifying the perception of self-movement: differences between the dominant and nondominant limbs

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Abstract: There is evidence that state estimation of the limb (e.g., position and velocity) during movement is less accurate for the nondominant limb compared to the dominant arm (Hore et al. 1996; Sainburg 2005). In this study we aimed to quantify possible perceptual differences due to state estimation by examining (1) the extent to which human subjects accurately estimated hand location without visual feedback during arm reaching movements and (2) how this ability compared for movements of the dominant (right) and non-dominant (left) hand. Right-handed human subjects used a robotic manipulandum to make 15 cm shooting movements with no visual feedback of the hand position. After movement completion, feedback in the form of two white circles located 3 cm apart appeared at one of four possible locations into the movement (3, 6, 9 or 12 cm). The circles flanked the actual movement trajectory, but were horizontally shifted from trial to trial (a shift between -1.5 and 1.5 cm in 0.1 or 0.2 cm steps). The magnitude of the shift was randomly determined from a uniform distribution, with the largest shifts (± 1.5 cm) resulting in one of the cursors being presented exactly on the movement path. Subjects were required to indicate which of the two circles represented the actual completed movement trajectory by making a two-alternative forced choice decision using a joystick located on the robot handle. Based on these responses we created psychometric functions to determine the perceived movement trajectory at the four locations along the movement path. Our results show that the perceptual estimate (bias) matched the direction of the movement bias; left-handed movements had a rightward movement and perceptual bias, with the opposite true for right-handed movements. The variability of this perceptual estimate also increased with distance into the movement, but was significantly and consistently greater for movements of the nondominant hand ($P < 0.01$). This was true even though the movement variability was equivalent between the two limbs ($P > 0.58$ for all cases). These results suggest that the perceptual estimation of nondominant limb position (based on a combination of proprioceptive and efferent copy information) is a more variable process than equivalent estimates made for the dominant limb. We hypothesize that this difference in perceptual variability between the two limbs might diminish for passive movements, as the judgement of limb position should be based more on equivalent proprioceptive information rather than efferent copy.

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Poster

804. Finger and Grasp Mechanisms

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Topic: D.17. Voluntary Movements

Support: NSF BCS-1153034 "Collaborative Research: Sensory Integration and Sensorimotor Transformations for Dexterous Manipulation"

Title: Tactile inputs distort perception of relative fingertip position

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Abstract: As we exert digit forces following contact with an object, the mechanical deformation of the finger pads elicits tactile afferent activity. The extent to which this tactile input alone might be used to estimate the relative position of the fingertips is unknown. We addressed this question by removing descending motor commands to generate digit forces while deforming the thumb and index finger pads by using a wearable haptic device. Subjects (n = 7) were asked to sense, remember, and match vertical and horizontal distances between the center of pressure (CoP) of the thumb and index finger pads (d_y and d_z, respectively). The digits were passively placed and held to a reference position (d_y = 0 mm, d_z = 64 mm) for 5 seconds. During this epoch, subjects were asked to sense the relative digit position while the haptic device exerted normal and tangential forces (*Fn*: 4.1-4.6 N and *Ftan*: 2.1-3.1 N, respectively) on each finger pad in either same (both up or down) or opposite (thumb-index: up-down or down-up) directions. After a 5-s break, subjects were asked to match the memorized d_y and d_z. We also examined effects of *Fn* magnitude exerted on the finger pads by using either the same range of *Fn* as for the above-mentioned conditions while exerting negligible *Ftan* (4.1-4.6 N, 0 ± 0.1 N), or negligible *Fn* and *Ftan* (< 0.1 N, 0 ± 0.1 N). Based on our prior work (Shibata et al. 2014), we hypothesized that estimation of d_y would be biased in the opposite direction of skin deformation, but only for the opposite digit *Ftan* direction condition. Subjects made systematic errors in reproducing d_y but only when the directions of thumb and index finger *Ftan* were opposite. Specifically, subjects positioned the thumb CoP lower than the index finger CoP when the *Ftan* of the thumb and index finger was directed upward and downward, respectively, and vice versa ($p < 0.05$). In contrast, d_z reproduction was accurate across all experimental conditions. These findings indicate that tactile input contributes to the biased estimation of relative digit position found when mechanical deformation of the fingertips is caused by the exertion of digit forces in opposite directions (Shibata et al. 2014). The relative contribution of tactile input and voluntary commands towards the biased estimation of relative digit position is currently being investigated.

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Poster

804. Finger and Grasp Mechanisms

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Topic: D.17. Voluntary Movements

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Title: Correlation between central EEG rhythms and fMRI-BOLD responses in the sensorimotor area during a unilateral motor task

Authors: ***K. UEHARA**[1], H. HOSHINO[1], Y. MIZUNO[1], K. KITA[1,2], L. M. LI[3], Y. OGATA[1], T. HANAKAWA[1];
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Abstract: A simultaneous EEG-fMRI measurement allows us to achieve an understanding of human brain function with both high temporal and spatial resolutions. Such multimodal brain imaging technique might provide further information on neural mechanisms underlying motor control in humans. It is well known that EEG alpha (8-13 Hz) and beta (14-30 Hz) rhythms in the central areas are functionally related to sensorimotor events and are modulated by a motor task or somatosensory input from the peripheral limb. However, functional relationships between central alpha and beta rhythms and fMRI-BOLD responses during a motor task are still unclear. Therefore, the aim of the present study was to identify whether central alpha and beta rhythms were correlated with BOLD signals during a motor task and, if so, whether there was any difference in their correlational characteristics between the both EEG rhythms. Simultaneous EEG-fMRI measurements were performed with a 3.0-T MRI scanner and a 32-channel MR-compatible EEG cap in 21 young healthy right-handed subjects. We asked the subjects to perform a unilateral finger-tapping task with their right index finger at five different frequencies (0.25, 1, 2, 3 and 4Hz) paced externally by auditory cues. The motor task lasted for 20 s, interleaved with a resting period for 20 s, in a semi-randomized block design paradigm. For the analysis of the EEG signals, gradient artifacts arising from MR pulses and ballistocardiogram artifacts were removed from the raw EEG signals. We then performed time-frequency analysis of the alpha and beta band EEG signals from the C3 electrode, corresponding to the sensorimotor area contralateral to the task side. Specifically, we used a wavelet analysis to obtain power time-

series for every TR epoch (2.5 s), yielding mean alpha or beta power in each task/rest block as a parametric modulator of a task. For the EEG-fMRI integration analysis, we used a general liner model to evaluate correlations of C3 alpha and beta signals with BOLD responses. The C3 alpha rhythms were inversely correlated with BOLD responses in the contralateral primary motor cortex, somatosensory cortex, superior and inferior parietal lobules and ipsilateral cerebellum during the unilateral finger-tapping task; however there was no positive correlation between EEG rhythms and BOLD signals. We failed to find correlations of the C3 beta signals with BOLD responses. The present study indicates that C3 alpha and beta signals may differ with respect to their correlations with BOLD signals during the motor tasks. Central alpha signals seem to be more sensitive to detecting BOLD responses than C3 beta signals, at least during the present tapping task.

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Poster

804. Finger and Grasp Mechanisms

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Title: Spatial variability in cortex-muscle coherence investigated with magnetoencephalography and high-density surface electromyography

Authors: *H. PIITULAINEN[1], A. BOTTER[2], M. BOURGUIGNON[1], V. JOUSMÄKI[1], R. HARI[1];
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Abstract: Objective Coupling between cortical magnetoencephalographic (MEG) signals with surface electromyography (sEMG) is referred to as cortex-muscle coherence (CMC). CMC is

strongest during isometric contraction but is, for unknown reasons, very weak or absent in about 20% of all individuals. Here, we aimed at evaluating whether the sEMG recording site or electrode derivation would explain some aspects of the CMC variability. Methods We used a novel non-magnetic high-density sEMG (HD-sEMG) electrode grid (36 mm × 12 mm; 60 electrodes separated by 3 mm) to record monopolar-sEMG signals from the right thenar simultaneously with 306-channel whole-scalp MEG recording from 14 subjects who kept for 4 min an isometric thumb abduction. CMC was computed using three HD-sEMG derivations (60 monopolar, 55 bipolar, and 32 Laplacian), and two derivations computationally produced from HD-sEMG signals to mimick conventional bipolar and monopolar sEMG recordings in terms of electrode diameter (9 mm) and inter-electrode distance (21 mm). Results Twelve out of 14 subjects showed statistically significant CMC in most of the HD-sEMG channels (on average 91-95% depending on the sEMG derivation), with maximum coherence (range across 12 subjects was 0.014-0.199 for monopolar derivation) at ~25 Hz. CMC was about a fifth stronger in monopolar than bipolar and Laplacian derivations (mean ± SD differences 19 ± 20% and 23 ± 11%, respectively). Moreover, the monopolar derivations resulted in the most uniform CMC distributions across the thenar (coefficient of variation: 19% for monoplar, 33% for bipolar, and 35% for Laplacian) and the most tightly clustered cortical sources in the hand area of the left rolandic cortex. Finally, the HD-sEMG derivations provided significantly stronger CMC than the conventional macroscopic bipolar (by 27 ± 28%, $p = 0.04$) and monopolar (by 19 ± 20%, $p = 0.02$) derivations. Conclusions These results demonstrate that the level of CMC, computed with respect to sEMG, depends on the sEMG-derivation but is not systematically affected by the recording site. The variability of the individual muscle anatomy therefore does not explain the large inter-subject variability in CMC level. Nevertheless, HD-sEMG recordings can facilitate detection of CMC. Monopolar sEMG resulted in strongest and most uniform CMC across the thenar and can thus be recommended for CMC recordings.

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Poster

805. Reach Control: Selection and Strategy

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Topic: D.17. Voluntary Movements

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Title: Spontaneous rebound in implicit sensorimotor learning can occur in the absence of sensory prediction errors

Authors: *S. D. MCDOUGLE, K. BOND, J. TAYLOR;
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Abstract: A popular model of human sensorimotor learning suggests that a fast process and a slow process work in parallel to produce the canonical learning curve (Smith et al., 2006). While a number of studies have pointed to potential neural substrates corresponding to these processes (Smith et al., 2006; Galea et al., 2011; Choi et al., 2014; Yang and Lisberger, 2014), a mechanistic account of the psychological underpinnings of the fast and slow process remains elusive. In a recent study (McDougle et al., 2015), we showed that explicit strategies and implicit learning map onto, respectively, the fast and slow processes put forth by Smith et al. (2006). Furthermore, we revealed that implicit learning itself can be subdivided, consisting of traditional trial-by-trial adaptation in addition to an operant process driven by repeated movements to unique regions of space. In the present study, we extend the investigation of the subcomponents of implicit learning, asking: What types of feedback drive the different components of implicit learning? And what are the different time-courses of these components? Here we show that implicit learning curves that closely match traditional cerebellar-driven, exponential adaptation curves can be produced using only abstract reward feedback in lieu of the standard spatial "sensory prediction error" feedback. Moreover, conventional markers of adaptation such as spontaneous rebound and aftereffects can also result from an operant subcomponent of implicit learning. We conclude that implicit motor learning is often a conflated measurement, consisting of both trial-by-trial calibration and operant directional biases. We suggest that future studies attempting to study single components of sensorimotor learning must isolate these subcomponents in order to skirt this conflation, by, for instance, varying the directions of movement or varying visual feedback.

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Poster

805. Reach Control: Selection and Strategy

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Topic: D.17. Voluntary Movements

Title: Validation of reaching movements made in a 2D virtual environment in typically developing children

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Abstract: The ultimate goal of rehabilitation is to improve movement kinematics which can be described at two levels: movement quality and motor performance. Measurement of change in movement quality and performance over time is also a method to identify motor learning. Motor learning is based on different principles which can be manipulated in treatment interventions by a therapist or through the use of interactive computer technology, such as virtual reality. Our aim was to compare the kinematics of movements in a physical environment to a similar virtual environment in typically-developing children. Participants (children; 8-17yrs) completed the Edinburgh Handedness Inventory to identify the dominant arm. They practiced reaching in the virtual environment to become familiar with the task. Then, they performed a series of 3 gestures (frontal, vertical and sagittal arm movements) in two environments: virtual and physical environments for a total of 6 gestures. 3D movement kinematics of the arm and trunk were recorded with 6 wireless electromagnetic sensors (G4, Polhemus, Vermont, 120Hz). Participants completed 15 trials of each gesture in each environment (45 trials per environment, for a total of 90 trials). The virtual environment consisted of an interactive game controlled by arm and hand movements (Jintronix, Montreal) projected on a computer monitor. Movements throughout the arm workspace were recorded with a Microsoft Kinect camera and projected into the game scene. Movements made in the virtual environment were less precise, slower and shorter in comparison to those made in the physical environment. In the virtual environment, participants used less trunk displacement in comparison to the physical environment. There were no significant differences between the two environments with respect to the range of motion of the elbow and the shoulder. Differences between movements made in each environment can be explained by less precise body position tracking in the virtual environment, decreased quality of the visual scene and differences in depth perception cues. The overall similarities of movements made in the two environments suggest that training in 2D game-like virtual reality environments may be feasible for motor rehabilitation of children.

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Poster

805. Reach Control: Selection and Strategy

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Title: Movement strategies used in full body reaching tasks to targets in real-world versus virtual environments

Authors: J. COST, R. PROCTOR, S. T. LEITKAM, M. E. APPLEGATE, C. R. FRANCE, *J. S. THOMAS;
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Abstract: The purpose of this study was to determine if movement kinematics of healthy individuals performing full-body reaches are different in a real-world environment (RW) compared to two distinct virtual environments. Nineteen subjects (11 male, 8 female) aged 18-35 performed full-body reaching tasks to static targets. In the RW reaches, the subject was instructed to reach and place a dodgeball on the targets (i.e., a shelf located in the mid-sagittal plane). The targets were positioned such that the subject (with elbows fully extended and shoulders flexed to 90 degrees) could, in theory, reach each target by flexing the hips 15, 30, and 60 degrees. In the 3D-TV reaches, the subject wore 3D shutter glasses and was oriented to their avatar on the 3D-TV in the third person perspective. In the Oculus Rift (OR) reaches, the subject wore a head mounted display and was oriented to their avatar in the first person perspective. In each virtual environment, the target was presented as a virtual ball co-located to the RW target coordinates. Holding a dodgeball in both hands, the subject was instructed to reach and touch the virtual ball. In 3D-TV and OR reaches, the subject received both auditory and visual feedback that contact with the virtual targets occurred. The 6-DOF location of the trunk and limb segments was streamed from eight Vicon Bonita cameras running Vicon Tracker software to MotionMonitor. The anterior position (AP), mid-position (MP), and height of the centroid of the fingertips, as well as joint excursions of the ankle, knee, hip, lumbar spine, shoulder, and elbow were analyzed using mixed-model MANOVAs with environment (RW,3D-TV, Oculus), target heights (high, middle, low) and trials as within subject factors, and sex as the between subjects factor. There was an effect of environment on AP and ML fingertip position ($p<0.05$). Follow-up analyses indicated no differences in fingertip position between 3D-TV and OR but there were significant differences between RW and 3D-TV and between RW and OR. In general, excursions of the hip and spine were greatest for reaches performed in OR and progressively less for the same reaches made in 3D-TV and RW. There was an interaction of gender and environment for ankle and knee excursions ($p<0.05$). In RW reaches female and male subjects used an ankle plantar flexion-knee extension pattern, but in the 3D-TV and OR environments, females used an ankle plantar flexion-knee extension pattern while males used an ankle dorsiflexion-knee flexion pattern. These findings suggest that the presentation of the virtual environment has a clear influence on joint excursions even when the endpoint of the effector is quite similar.

Disclosures: **J. Cost:** None. **R. Proctor:** None. **S.T. Leitkam:** None. **M.E. Applegate:** None. **C.R. France:** None. **J.S. Thomas:** None.

Poster

805. Reach Control: Selection and Strategy

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Program#/Poster#: 805.04/U13

Topic: D.17. Voluntary Movements

Support: NIH R21AR064430

Title: Effects of avatar presentation and display environment on game perception and lumbar motion in virtual dodgeball

Authors: ***M. E. APPLEGATE**, S. T. LEITKAM, J. COST, R. PROCTOR, C. R. FRANCE, J. S. THOMAS;
Ohio Univ., Athens, OH

Abstract: The purpose of this study was to assess both cognitive and physical responses to our newly developed game of virtual dodgeball in healthy adults aged 18-35. The game environment, developed using Vizard software, was a basketball arena in which the subject played dodgeball against four virtual opponents. The game was played in two distinctly different virtual environments. In the 3D-TV environment, the subject wore 3D shutter glasses and was oriented to their avatar on the 3D-TV in the third person perspective. In the Oculus Rift (OR) environment, the subject wore a head mounted display and was oriented to their avatar in the first person perspective. Virtual balls were launched in a randomized order from each of the four opponents to varying target locations in order to shape lumbar motion. The ball trajectories were set such that they would make contact with the subject's body anywhere from the mid-shank to the head. The subject scored points by successfully blocking and ducking launched balls. Game play consisted of three levels of difficulty, each with two sets of 15 launched balls. The levels progressively became more difficult by lowering the projected contact height of the launched balls. Body movements were streamed from Vicon Tracker to MotionMonitor, which parameterized game conditions (e.g., ball trajectories, scoring), communicated with Vizard, and recorded segment kinematics and game outcomes. Following each game, the subject completed the NASA Task Load Index. Cognitive data were analyzed using paired samples t-tests. For each game level, lumbar motion was analyzed using a repeated measures MANOVA; environment (3D-TV, OR), level (3), and sets (2) were the within subject factors. Perception of task success was significantly higher and frustration rates were significantly lower in the OR environment

compared to the 3D-TV environment ($p < 0.05$). Across all game levels, success rate in the OR environment was 85% compared to 69% for 3D-TV environment. Levels of engagement and immersion were also higher in the OR environment compared to the 3D-TV environment ($p<0.05$). Lumbar excursions increased at each level of game play ($p < 0.05$); lumbar motion in the OR environment ranged from 33.0-43.4 degrees, while lumbar motion ranged from 17.6-29.6 degrees in the 3D-TV environment. Adjusting parameters in virtual dodgeball increased lumbar motion in healthy subjects, and for each game level, lumbar motion was greater in the OR environment compared to the 3D-TV environment ($p<0.05$). Virtual environment is an important factor for both cognitive and motor behavior in the implementation of a gaming environment for research endeavors as well as treatment interventions.

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Poster

805. Reach Control: Selection and Strategy

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Topic: D.17. Voluntary Movements

Title: Performance asymmetries for left and right arms in 3D vary by visual condition and spatial location

Authors: T. A. AMEDEE[1], V. G. DONZE[1], A. PRZYBYLA[2], *J. M. HONDZINSKI[1]; [1]Kinesiology, Louisiana State Univ., Baton Rouge, LA; [2]Kinesiology, Pennsylvania State Univ., University Park, PA

Abstract: People often produce greater endpoint accuracy in normal room lighting when reaching toward remembered targets on a horizontal plane with the dominant right arm compared to the non-dominant arm. Interestingly, people can produce greater or similar endpoint accuracy when reaching toward remembered targets in darkness with the non-dominant arm compared to the dominant arm. Researchers blame asymmetric cortical control for these differences, suggesting that the right hemisphere possesses a more robust control strategy for such accuracy. In this study we questioned whether these hemispheric differences would also exist for 3D pointing movements primarily performed in vertical planes. We chose 3D movements as people often vertically undershoot remembered target locations when reaching with their dominant limb in darkness relative to an illuminated environment and in some cases can be more accurate without vision. Young healthy adults produced straight arm pointing movements to real targets

and remembered target locations in complete darkness (DARK) or normal room lighting (LIGHT). Gaze was anchored on target or remembered target locations during the pointing movement. Nine targets were located on a flat vertically oriented surface at a 1.5 m in front of subjects. Target levels included the shoulder and shoulder +/- 3o cm; three directly in front of each subject's midline and three 30 cm right and 30 cm left of midline. Subjects placed the hand of their extended arm on the thigh. Pointing movements were performed to each target in each visual condition. Pointing movements to each of 6 non-target locations in each visual condition were also performed to help ensure subjects did not memorize target locations. Movements of the shoulders, ankles, and the fingertip of the pointing limb were recorded at 60 Hz. Absolute 3D angular error for each remembered reach was determined relative to average reaches for real targets for a given target and subject. Subjects often ended pointing movements in the DARK vertically below those in the LIGHT thus the phenomenon of undershooting remembered target locations in darkness exists for both arms. In the LIGHT condition endpoint errors for the dominant arm were more often less than or similar to those for the non-dominant arm. In the DARK condition errors between arms varied among subjects, however, were commonly smaller for the non-dominant arm for targets below shoulder level left of midline. These data provide some evidence to support hemispheric specialization; specifically, that the right hemisphere offers significant control over 3D endpoint accuracy when vision is not available.

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Poster

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W911QY-12- C-0078 ProjectDoD,USA"Consequences of Loading on Postural- Focal Dynamics

Italian Ministry of Foreign Affairs

Title: Hybrid control of force and position in a sliding task

Authors: *D. DE SANTIS[1], C. PASQUINELLI[2], P. MORASSO[1], V. SQUERI[1], M. CASADIO[2];
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Abstract: A general question is to what extent position and force control are independent processes and/or in which manner they can be linked according to a common goal. This work aimed at investigating the mechanisms of motor control in a hybrid task that requires a concurrent control of force and position. With this purpose, seven subjects (30 ± 6 years old) were asked to slide a deformable virtual object for 15 cm along a haptic-rendered vertical wall using a 2-DOF manipulandum in three different experimental conditions: i) the mean sliding speed was imposed (0.14 - 1.25 m/s), but the object was unbreakable, making the contact force a free variable, ii) the object was fragile so that the maximum applicable force was constrained (1.5 - 4 N), but there was no imposed limit on the sliding speed, iii) the object was fragile and subject to a gravitational force (1.5 N) opposed to the sliding motion, with no constraint on the sliding speed. In order to characterize the strategy adopted by the subjects as a function of the constraints, the performance was quantified in terms of mean value (Fa) and variability (deviation from the mean - Fv) of the applied contact force, as well as in terms of average sliding speed (Vm). In the presence of an explicit velocity constraint, but no particular force constraint (condition i), the average magnitude of the force was independent of the speed of movement, while the force variability increased when moving at faster speeds (Vm < 0.1 m/s: Fa = 2.07 ± 1.03 N, Fv = 0.47 ± 0.24 N; Vm > 0.2 m/s: Fa = 2.48 ± 0.91 N, Fv = 1.11 ± 0.53 N). When a force constraint was explicitly introduced (condition ii), all the subjects reduced the average force from 2.13 ± 1.00 N to 1.04 ± 0.43 N and consistently decreased both their sliding speed and force variability proportional to the applied force. Fv was lower (0.30 ± 0.11 N) than before (0.47 ± 0.24 N) for matching average speeds, suggesting a dependency on Fa. When we introduced the gravitational force (condition iii), variability seemed to be a limiting factor: only the 3/7 subjects who changed sliding strategy succeeded for forces below 2.5 N. Instead of minimizing the force variability, they increased the speed so as to balance the effect of the gravity and apply a lower average force. Several studies tested the hypothesis that individuals improve their performance by seeking solutions that are robust to perturbations to reduce the influence of their intrinsic noise. The results of the proposed experiment seem to support this finding, suggesting that noise in the control of force may have acted as a constraining factor that induced the subjects to explore the space of possible solutions to minimize the impact of their variability.

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Poster

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Topic: D.17. Voluntary Movements

Support: Grant-in-Aid for JSPS Fellows

Title: Toward identification of neural-pattern transition of limb selection using ongoing electroencephalogram

Authors: *K. AMEMIYA[1,2], J. IZAWA[3], J. USHIBA[1], R. OSU[4];
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Abstract: Action selection, a process of choosing one from all possible conflicting motor plans, is central to generate motor movements in our daily life. For instance, selecting right or left arm in order to reach to a given target might request the brain to decide whether the selected hand is more valuable than the other option with taking account of the perceived target position. When the target is provided near the right hand, one might choose the right hand more whereas, when it is near the left hand, one should choose left hand more. A question is how these two options would compete together in the decision making process in the brain when the target is provides in between the right and the left hand. We hypothesized that neural activities prior to making decision might affect a competition process between two options so that the EEG signals would predict which option the brain would select near future. To test this hypothesis, we measured the whole head 64ch EEG (Active-Two, Biosemi system, Amsterdam) during subjects executing a reaching task. In this task, participants were required to reach with one hand to a target that appeared at a variable location on a semicircular array. We classified the limb selection with Support Vector Machine using EEG signals of the fixation period (2000 ms), which is preceded by target representation. In addition, we compared the decoding results between center target condition and peripheral target condition. We found that the classification accuracies of predicting limb reached to as high as 80% in case of center target condition. In contrast, the classification accuracies of same data only reached about 63% in case of peripheral target condition. In 7 out of whole 13 subjects, the variance of decoding accuracies was significantly different between two conditions. In addition, in order to know the transition of limb selection process, we divided fixation period into 4 time windows and averaged maximum decoding accuracy of each participants every 4 periods. Averaged maximum of decoding accuracy was also significantly different between conditions and in first and last period out of 4 time periods.

These results indicate that influence of ongoing activity on subsequent decision fluctuate time to time, but both time period of soon after the previous trials and time period right before the target presentation contribute to subsequent limb selection.

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Poster

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Topic: D.17. Voluntary Movements

Support: ARC Fellowship (FT120100391)

ARC Fellowship (DE120100653)

Title: Manipulation of movement preparation time reveals a target-selection component to use dependent learning

Authors: ***T. J. CARROLL**, E. POH, H. ALAVI, S. RIEK, W. MARINOVIC;
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Abstract: Movements tend to be biased towards the direction of previously executed actions, but it is unclear to what extent these effects are due to movement planning versus movement execution processes. Here we manipulated the predictability of target locations and the time available to process target location information, in order to dissociate between two potential sources of such systematic aiming errors: a) recent movement history and b) the expected location of the next target. In two experiments, aiming errors were measured for isometric wrist forces made toward targets presented occasionally (15-20% of trials) at angles at + 90° from the centre of a distribution of targets centred on 45° (Exp 1 SD = 7.5°; Exp 2 SD = 15°). Movement preparation time was controlled using the timed response paradigm (Exp 1) or a reaction time task (Exp 2). Aiming bias increased monotonically as probe target angle departed from the centre of the target distribution when movement preparation time was short, but not when movement preparation time was long. The sensitivity of bias to the timing of stimulus presentation suggests a mechanism related to movement preparation, rather than to movement execution. However the data do not distinguish between the potential influence of expected target location and movement history, because the most frequently repeated target was also the most probable next target. We therefore designed a third experiment to directly dissociate the influence of these two putative

sources of bias, by requiring subjects to perform a sequence of two movements on each trial. The first movement was made to one of three potential target locations at 25° (20% of trials), 45° (60%) or 65° (20%), whereas the second movement was made to a fixed-target, either at 0° or 45°, in separate blocks. When the fixed target direction was at 45°, aiming errors toward uncertain targets were biased toward the central, more probable target, and this effect was larger for short than for long preparation times. When the fixed target was at 0°, the distribution of errors toward uncertain targets was identical, but offset toward the second movement on the preceding trial. Moreover, this offset in bias was identical irrespective of the movement preparation time. This shows that a tendency to make errors toward the most likely next target interacts with a tendency for movements to be biased towards the most recently executed action. Moreover, these two sources of movement bias are dissociable on the basis of movement preparation time; bias due to movement history is insensitive to movement preparation time, whereas bias due to target selection is much greater when preparation time is constrained.

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Poster

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Support: NIH Grant R21AR064430

NIH Grant R01AT006978

Title: Virtual reality display influences dynamic movement patterns in gaming-based research

Authors: ***S. T. LEITKAM**, R. PROCTOR, J. COST, M. E. APPLEGATE, C. R. FRANCE, J. S. THOMAS;
Ohio Univ., Athens, OH

Abstract: The purpose of this study was to determine if the type of display used in a virtual reality (VR) game affected the movement patterns used in performing a kinematically redundant dynamic task. A VR dodgeball game was played by 18 subjects (aged 18-35) on two distinctly different displays. In the 3D-TV display, the subject wore 3D shutter glasses and was oriented to their avatar on the 3D-TV in the third person perspective. In the Oculus Rift (OR) display, the

subject wore a head mounted display and was oriented to their avatar in the first person perspective. The subject scored points by successfully positioning the virtual ball held in both hands to intercept each launched ball. Thus, this task required both appropriate joint excursions and the correct timing of these excursions to block the launched ball. The impact locations were scaled to the anthropometrics of each subject to normalize the amount of theoretical lumbar flexion required to block each launched ball. For each subject, the impact locations of the launched balls were randomized, but identical for the games played in each display. Thus, in theory, the excursion patterns required to successfully block the launched balls in each display would be identical. The kinematics, as measured with Vicon Bonita cameras and MotionMonitor, were defined by angular excursions between a neutral posture and posture at time of intercept of the launched ball. Flexion of the ankle, knee, hip, lumbar spine, shoulder, and elbow were analyzed. In addition, the position of the centroid of the hands at intercept of the launched ball was extracted. Mixed-model MANOVAs were performed with display (3D-TV, OR) and projected impact location (high, middle, low) as within subject factors and sex as the between subjects factor. Joint excursions of the knee, hip, lumbar spine, and shoulder were greater in OR compared to 3D-TV ($p<0.05$). At intercept, the vertical and lateral hand positions showed no difference between the two displays, but the anterior hand position was on average 16.5 cm closer to the body in 3D-TV compared to OR ($p<0.05$). When playing dodgeball with the OR, for any given impact location, subjects chose to intercept the balls further away from their body compared to games played 3D-TV. Thus, display type resulted in angular excursions that were very different for successful intercepts of balls launched to the same location. These results together show that the type of display used in a VR game will have a significant effect on the kinematic patterns used to play the game. Specifically, greater overall angular movement is expected for VR games with first person perspective in comparison to 3D-TV games with a third person perspective.

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Poster

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Topic: D.17. Voluntary Movements

Support: NINDS Grant R01 NS084948

Title: Movement kinematics while choking under pressure

Authors: *P. A. BUTCHER[1], T. G. OSBORNE[1], T. G. LEE[2], J. A. TAYLOR[1];
[1]Psychology Dept., Princeton Univ., Princeton, NJ; [2]Psychology Dept., Univ. of California, Santa Barbara, Santa Barbara, CA

Abstract: Performance typically improves with increased arousal or incentives, however, in some instances, if the incentive becomes too large, performance can dramatically decrease, an effect colloquially known as choking under pressure. Experimental investigations of choking under pressure have generally framed it as a discrete cognitive phenomenon, pointing to interplay between the executive function in the frontal cortex, and midbrain reward regions. However, it remains an open question as to the effect on movement execution. For example, is a basketball player who misses the game winning free-throw despite being an excellent free-throw shooter just releasing the ball too early or too late, or are the kinematics of the actual shooting motion changed? We investigated choking under pressure by manipulating monetary incentive in a reaching task, which required placing a cursor into a virtual target between 450 and 550 ms. At the start of each trial, participants (N=31) were informed that each trial was prospectively worth either $2, $5 or $20. At the end of the experiment one trial was picked at random and performance on that trial determined whether the bonus received _ a method purported to maintain consistent motivation. Heightened motivation should result in an increase in performance from low to mid incentives, but a decrease in performance from mid to high incentives would suggest choking under pressure. Importantly, the increase from low to mid incentive serves as an internal control to separate participants who are motivated by monetary incentive from those who are unmotivated. Thus, we separated our participant pool into motivated and unmotivated groups. We find that approximately half of the participants (N=16), were motivated by the increase from $2 to $5 and, importantly, on $20 trials, they displayed a precipitous drop in performance (i.e., choking). In contrast, the unmotivated participants showed no difference in performance on high value trials. Our primary focus was to identify what kinematic features of their movement had changed between $5 and $20 trials. However, despite comparing: reaction time, movement time, peak speed, position, and force, and consistent with previous literature (Lee et al 2014) we were unable to find a consistent kinematic signature of choking under pressure. This result presents a puzzle, how does a consistent difference in behavior, in this case impaired performance at high incentives, not result from a kinematic difference? Should these findings persist, one possible interpretation would be that impaired performance under pressure may be the result of processing involved in the selection of an action, but not in the execution.

Disclosures: **P.A. Butcher:** None. **T.G. Osborne:** None. **T.G. Lee:** None. **J.A. Taylor:** None.

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Topic: D.17. Voluntary Movements

Support: R01 NS084948

Title: Explicit aiming strategies are fundamental to learning in a visuomotor adaptation task

Authors: *K. BOND, J. TAYLOR;
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Abstract: There is mounting evidence for the idea that performance in a visuomotor rotation task can be supported by both implicit and explicit forms of learning. The implicit component has been well-characterized in previous experiments and is thought to arise from the adaptation of an internal model driven by sensory prediction errors. However, the explicit contribution is less well-defined and previous investigations have relied on indirect measures such as dual-task manipulations, post-tests, and descriptive computational models. To address this problem, our lab developed a new method to directly assay explicit learning by having participants verbally report their intended aiming direction on each trial. While our previous research employing this method demonstrated the possibility of measuring explicit learning over the course of training, it was only tested over a limited scope of manipulations common to visuomotor rotation tasks. In a recent study, we sought to better characterize explicit and implicit learning over a wider range of task conditions (Bond and Taylor, 2015). Specifically, we tested how explicit and implicit learning change as a function of visual landmark configuration, training target number, and rotation size. We found that explicit learning was remarkably flexible, responding appropriately to task demands. In contrast, implicit learning was strikingly rigid, with each condition producing similar degrees of implicit learning. To further test the notion that explicit learning may be fundamental to learning in a visuomotor rotation task, we sought to determine if explicit learning was also responsible for structure learning (Braun et al. 2009). In a structure learning paradigm, the rotation magnitude changes frequently throughout training but has a zero mean. Following structure training, participants show faster learning of a novel, consistent rotation relative to participants without structure training. For our current experiment, we combined this paradigm with our method of assessing aiming strategies during training. We found that structure learning is almost entirely explicit, with little contribution from implicit learning. This evidence reinforces the conclusion that explicit learning is a fundamental, flexible element of learning in visuomotor adaptation tasks.

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Poster

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Title: Improvements in visual search contribute to visuomotor learning

Authors: *C. PERRY;
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Abstract: Christopher Perry1, Tarkeshwar Singh1, Kayla Goins1, Barbara Marebwa1,2, and Troy Herter1 1University of South Carolina, Columbia, SC, USA 2University of Trento, Trento, Italy Introduction: Visual search is used to gather visual information by actively scanning the visual environment with eye movements (overt visual search) and peripheral vision (covert visual search). Previous studies have shown that visual search can improve with practice and expertise in motor skills is linked to efficient visual search. While these findings suggest that improvements in visual search may contribute to motor learning, previous research has not directly tested this hypothesis. Here we examine the extent to which improvements in visual search contribute to the acquisition of a novel visuomotor skill. Methods: Eighteen young adults (20-31 years old) practiced a bimanual visuomotor task (Object Hit and Avoid Task) using an upper-limb robotic device (KINARM Endpoint Lab, BKIN Technologies, Kingston, Canada). In this task, objects (eight distinct geometric shapes) moved towards the subjects who used virtual paddles displayed on each hand to hit away two target shapes (Targets; n = 200), and avoid hitting the six distractor shapes (Distractors; n = 100). Each task trial lasted approximately two minutes, and the shape, location, and movement speed of individual objects was varied randomly to ensure every task repetition was distinct. Subjects completed six repetitions of the task once a week for six weeks. Object shapes assigned to Targets and Distractors varied weekly. Eye and hand movements were recorded to investigate the influence of visual search and limb-motor control on task performance. Results: Task performance, as measured by Targets hit and Distractors avoided, increased across all six weeks. Task performance improved rapidly during the first week (acute phase) followed by slower improvements over the over 5 weeks (chronic phase). We observed that acute improvements were more coupled to the number of targets that were overtly viewed with smooth pursuit and the number of targets that were successfully hit

following pursuit (overt success). Furthermore, chronic improvements appeared to be more linked to increases in success avoiding distractors and hitting targets that were viewed peripherally (covert success). Improvements in task performance did not appear to be coupled to changes in limb motor control. Conclusions: These results provide direct evidence that improvements in visual search can contribute to visuomotor learning. Our data also shows that both overt and covert visual search contribute to motor learning during acute and chronic phases, respectively.

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Poster

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Title: Moving Slowly is Hard for Humans

Authors: ***N. HOGAN**[1], H. MARINO[2], S. K. CHARLES[3], D. STERNAD[4];
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Abstract: Human dexterity exceeds that of modern robots, despite vastly slower 'hardware' (muscle) and 'wetware' (neural processing and transmission). Mounting evidence suggests this is due to using dynamic primitives, generated with minimal central supervision as attractors of dynamic neural networks. Dynamic primitives include discrete and rhythmic movements and imaging studies show that they evoke activity in substantially different brain regions. However, advantages of control using dynamic primitives may be offset by compromised versatility. We recently showed that unimpaired humans could not sustain discrete motions as duration decreased, and that could not be attributed to biomechanical limitations. This complementary study tested whether smoothly rhythmic performance could be maintained as movement period increased. Ten seated unimpaired subjects performed horizontal plane movements of their dominant hand between two target positions. Belts restrained shoulder motion; a brace discouraged wrist motion. Hand motions were recorded and displayed on a screen. Targets were displayed as large circles (5cm radius) to de-emphasize accuracy. Targets were located in a mid-sagittal plane specifying a movement distance of 28cm in the approximate center of the upper-limb workspace. Subjects were instructed to perform smoothly rhythmic back & forth movements between targets in synchrony with computer-generated sounds (1 per back & forth cycle) but without stopping at the ends, i.e. with no dwell time. Each trial began with 10 sounds at 1s intervals; then 25 sounds where each interval increased by 200ms; then 5 sounds at 6s intervals; then another 25 sounds where each interval decreased by 200ms; then 10 sounds at 1s intervals. Subjects performed this sequence twice with eyes open and twice with eyes closed. Subjects successfully executed this movement sequence. Remarkably, with eyes closed or open, the shape of their hand speed profile changed dramatically with duration, becoming visibly more irregular as movement slowed. Increased irregularity was accompanied by increased dwell time at the extremes of displacement; subjects did not sustain smoothly rhythmic motion. Measured velocity profiles were parsed into a sequence of overlapping submovements, each with a stereotyped shape (support-bounded lognormal). The number of submovements increased systematically with duration. These results show that it is hard for humans to execute smoothly rhythmic motions slowly, and this cannot be attributed to biomechanical factors. Instead they 'default' to using another dynamic primitive, and compose motion as a sequence of overlapping 'discrete' actions.

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Topic: D.17. Voluntary Movements

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NSF CMMI 1200830

NSF SES 1230933

Title: The subjective value of effort explains preferred movement speed

Authors: *E. SUMMERSIDE, A. AHMED;
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Abstract: In economics, it is well-known a reward's subjective value can differ from its objective amount. However, every reward requires an effort to obtain it and we currently do not have a good understanding of how effort costs are subjectively valued in healthy adults. In the current study we used an economic approach to quantify how individuals subjectively valued effort, where we quantify effort as the metabolic cost required to perform the movement. We then attempted to use these measures to explain the variability in movement preferences observed across individuals. Based on current theories in motor control, we hypothesized that individuals who exhibited greater sensitivity to effort costs would exhibit slower preferred movement speeds. Specifically, sensitivity to effort would be inversely related to preferred movement speed. Participants (n=20) visited the lab for two separate sessions. The first session involved performing seated 20cm out-and-back arm reaches. Metabolic rate was measured via expired gas analysis as participants reached against five resistances. In the second session, they were instructed to choose between a sure bet of performing a low effort reach or risk performing a higher effort reach. The risky choice was presented as a percentage value paired with one of the resistances. The percentage represented the chance of having to reach at the presented resistance for 5 minutes with the alternative outcome being to sit quietly for 5 minutes. Using the metabolic and individual choice data, the subjective value of effort (SV) was calculated based on Cumulative Prospect Theory (CPT): $SV(x) = x^{\alpha}$. Here, x is the metabolic cost, and α is the nonlinearity in effort valuation. An $\alpha > 1$ signifies overvaluation of effort, an $\alpha < 1$ signifies undervaluation and an $\alpha = 1$ signifies an objective valuation. In six participants, preferred reaching speed (m/s) was measured before the first session. A model-selection analysis revealed a significant distortion on an individual basis, with seven participants overvaluing effort. $\alpha > 1$, and eight undervaluing effort, $\alpha < 1$ ($p < 0.05$). We also observed a significant correlation between a participant's preferred reaching speed and their subjective valuation of effort ($R^2 = 0.67$, $p = 0.02$). Specifically, the greater a person's sensitivity to effort (increasing α) the slower they preferred to reach. Together these findings present a novel approach to quantifying effort costs that provide a unique window into how physical effort is considered when forced to decide between effortful movements and ultimately how those movements will be performed.

Disclosures: E. Summerside: None. **A. Ahmed:** None.

Poster

805. Reach Control: Selection and Strategy

Location: Hall A

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Topic: D.17. Voluntary Movements

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NSF Grant SES1352632

Title: Effort, reward, and vigor in decision-making and motor control

Authors: *R. SHADMEHR[1], H. J. HUANG[2], A. A. AHMED[3];
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Abstract: Decisions depend on the reward at stake and the effort required. However, these same variables influence the vigor of the ensuing movement, suggesting that factors that affect evaluation of action also influence performance of the selected action. Here, we describe a mathematical framework that links decision-making with motor control. Each action has a utility that combines the reward at stake with its effort requirements, both discounted as a hyperbolic function of time. The critical assumption of our model is to represent effort via the metabolic energy expended to produce the movement. This energetic representation describes a parameterization of effort as a function of movement duration, mass of the limb, distance, and force, which we confirmed experimentally in reaching movements. The resulting model makes predictions regarding how these variables would affect decision-making and motor control. We found that the framework provided insights into the following observations: 1.Subjects not only preferred the more rewarding stimulus, but also moved faster toward it. 2.Subjects preferred to reach to the stimuli that required transport of a smaller mass, but did so with higher vigor than when forced to make the same amplitude movement with a larger mass. 3.Subjects were willing to perform actions that required greater effort, but only in exchange for greater reward. However, they moved with less vigor when forced to perform the less preferable action. 4.Increasing the duration that subjects had to wait before making a movement reduced the vigor of the ensuing movement. 5.In a task in which there were objective measures of reward and effort via their caloric values, subjects chose actions which were consistent with a utility in which reward and effort were both discounted by the duration of the action. 6.As the duration of generating an isometric force increased, the utility of effort did not continue to increase, but rather reached a

plateau. 7.Natural walking speed, and well as the speed of performing other actions, varied with the city in which people lived. Our main result is to show that a single mathematical formulation of action, a utility describing the goodness of the movement via effort, reward, and time, predicts both the decision that animals make as well as the vigor of the movements that follow. This framework accounting for choices that birds make in walking vs. flying, choices that people make in reaching and force production, and the curious fact that pedestrians walk faster in certain cities. We suggest that decision-making and motor control share a common utility in which the expected rewards and the energetic costs are discounted as a function of time.

Disclosures: **R. Shadmehr:** None. **H.J. Huang:** None. **A.A. Ahmed:** None.

Poster

805. Reach Control: Selection and Strategy

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Eric P. and Evelyn E. Newman Fund

Gloria Blake Fund

Title: Predictability in the control of complex object dynamics

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Abstract: Numerous studies on reaching showed that humans compensate for the nonlinear inertial dynamics of the skeleton and imposed force fields. However, the dynamics of even simple objects can be vastly more challenging: fluid sloshing in a cup of coffee generates prodigiously complex forces. In addition, human limb dynamics interact with such object dynamics in highly counter-intuitive ways. How do humans predict and compensate for this complex behavior? Or do they preempt and avoid it? Previous research by our group showed that humans reduce the complexity of the hand-object interactions, rendering the behavior more

predictable. This study examined rhythmic motion of an object with internal dynamics with a focus on the resonance structure of the coupled hand-object system. The task of carrying a cup of coffee was simplified to the 2D cart-and-pendulum model and implemented in a virtual environment where a ball represented the liquid rolling in a semicircular cup manipulated by the subject. The dynamics of cup-and-ball interacting with the human limb include two resonant peaks and an anti-resonance, the latter determined only by the pendulum: periodic forces applied at this frequency yield zero cup motion. Subjects moved the cup-and-ball system rhythmically, at 8 different metronome frequencies between 0.7 and 1.2Hz; in 8 interspersed trials subjects were instructed to move at their preferred frequency. This same set of frequencies were performed with the nonlinear cup-and-ball system and a linearized version of the same system to understand the challenge due to the nonlinearity. Subjects were free to choose their cup and ball amplitude. We hypothesized that humans choose strategies to maximize predictability by avoiding anti-resonance and seeking resonance of the coupled hand-object system. Because lower forces have less noise and afford more precise control, moving at resonance reduces required forces and increases precision and predictability; the converse applies to anti-resonance. An additional option (applicable to the nonlinear model) is to avoid nonlinearities by choosing the smallest possible ball motion to linearize the system. Results showed that in self-selected frequencies subjects adopted one of the two resonance frequencies. The amplitude of the ball movement became smaller with practice. In the paced trials subjects synchronized with the metronome, although the variability depended on the frequency: the closer to anti-resonance, the higher the variability. These results present first insights into how human dexterously control complex objects, which is of high clinical significance as many daily activities involve object manipulation.

Disclosures: D. Sternad: None. **I. Zuzarte:** None. **N. Hogan:** None.

Poster

805. Reach Control: Selection and Strategy

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Topic: D.17. Voluntary Movements

Support: Marriner S. Eccles Foundation

Utah State University Office of Research and Graduate Studies

Utah State University Center for Persons with Disabilities

Title: Exploring a more functional task for studying upper extremity motor control

Authors: *C. R. HENGGE, J. R. PIERCE, K. E. TEW, S. Y. SCHAEFER;
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Abstract: The paradigm of point-to-point reaching has been widely used to study upper extremity motor control in a number of typical and clinical populations. Although it is viewed as a proxy for goal-directed movements, it may be limited in its approximation of how arm and hand movements are controlled in the real world. We have begun to develop a functional motor task that adds manipulation, tool use, object transport, and executive function to the established 'gold standard' of point-to-point reaching. Thus, the purpose of this study was to determine the construct validity of our functional task in a sample of healthy adults. In this case, the existing method against which we compared our task was a targeted reaching task. In two different tasks, 28 adults (mean±SD age: 20.4±2.2 years) performed planar out-and-back movements of 16 cm in three different directions (45°, 90°, and 135°) relative to constant start location along midline using their nondominant arm. In the 'gold standard' reaching task, participants moved a digital cursor sequentially between targets that were virtual squares displayed on a computer screen, veridical to the planar workspace. In the functional task, participants manipulated a spoon to transport beans sequentially between targets that were actual cups anchored to the planar workspace. In both tasks, the primary measure of performance was movement time, which indicated the time to complete five repetitions to each target. Mean performance on the functional task was not correlated with that of the reaching task (Spearman's rho = -0.039; p=.84). The variable of movement time was, however, highly sensitive and specific to performance on each task, as the area under the Receiver Operating Characteristic (ROC) curve was 0.95. Additional measures of performance, such as cumulative hand distance (rho = .04; p=.83) and inter-repetition interval (rho = 0.0016; p=.99), were also poorly correlated between the two motor tasks. These results demonstrate a lack of construct validity between the functional task and the established point-to-point reaching paradigm in healthy human participants, thereby suggesting that 1) the functional task may recruit different neural mechanisms recruited to perform the additional aspects of the functional task (e.g. object manipulation) and 2) these mechanisms may be measurable by psychophysical experimentation. Thus, the functional task tested in this study may be used in the future as a relevant proxy for studying real-world upper extremity motor control.

Disclosures: **C.R. Hengge:** None. **J.R. Pierce:** None. **K.E. Tew:** None. **S.Y. Schaefer:** None.

Poster

805. Reach Control: Selection and Strategy

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Topic: D.17. Voluntary Movements

Support: NIH NICHD R01HD053727

Title: Age differences in muscle activation patterns supporting arm stabilization

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Abstract: Sensorimotor function often becomes degraded with aging and this change has been linked to a decline in whole-body postural stabilization and concomitant increase in fall risk. One way people avoid falls is to reach and grasp a railing or other object with which to stabilize the body. Success requires accuracy of the reach and efficacy of the stabilization effort. Here we emulate that scenario in an arm stabilization task that allows us to characterize neuromuscular control while minimizing fall risk. Three groups of healthy subjects (young: 18-29 yrs, n=4; middle: 30-59 yrs, n=3; older: 60-90 yrs, n=8) sat in front of a horizontal planar robot and grasped its spherical handle. Subjects were to stabilize the handle at a 1 cm dia. target location while the robot produced one of three types of force perturbations: a force vector rotating predictably in the x-y plane (0.2 Hz), unpredictable sum-of-sinusoid forces (1.1, 1.2, 1.65 & 1.75 Hz), and a combination of both. Subjects completed 18 trials of 60 s each. On half, subjects received real-time visual cues showing the target and feedback of the robot handle location; on the other half, no handle feedback was provided. We measured handle x-y position in each trial and computed kinematic error. We also measured electromyographic (EMG) signals from shoulder and elbow muscles. EMG signals were zero-mean rectified, low-pass filtered and normalized to MVC. Muscle pairs were used to calculate 2 measures of joint coordination at the shoulder and at the elbow: agonist / antagonist coactivity (CoA) and reciprocal activation (ReA). To evaluate the neuromotor response to the perturbations, we evaluated the power spectra of these EMG signals at the perturbation frequencies. As anticipated, subjects stabilized with more kinematic error without visual feedback than with visual feedback; no other age group or condition differences were found in the kinematic data. However, neural control strategy varied across age groups. Analysis of shoulder and elbow CoA power at high perturbation frequencies (>1 Hz) found that older adults allocated a larger percentage of their available EMG dynamic range to agonist/antagonist muscle coactivation than did the younger two groups. By contrast, younger adults demonstrated larger power in ReA, especially in the muscles controlling the shoulder at the lowest frequency (0.2 Hz). Thus, our results suggest that younger adults used a postural control strategy favoring reciprocal activation over coactivation in this task whereas

older adults used a coactivation strategy. Future studies are planned to explore factors contributing to this aging-related shift from reciprocal to coactive neuromuscular control.

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Poster

805. Reach Control: Selection and Strategy

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Topic: D.17. Voluntary Movements

Support: DFG SFB 889 - C5

BMBF 01 GQ 1005C

Title: Effort discounting in reaching favors short-duration over short-distance movements

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Abstract: When deciding between alternative options, a rational agent chooses on the basis of the desirability of each outcome and the cost associated with each decision. In behavioral economics, this is conceptualized by the expected utility of each option, which can be discounted by unfavorable factors, such as the delay with which a reward is obtained. As different choices typically results in different actions, the effort associated with each action also has to be taken in account. In previous studies, a discounting of physical effort has been observed (Kurniawan et al. 2010) and characterized (Körding et al. 2004, Hartmann et al. 2013). However this physical effort discounting function has only been studied using isometric force productions, and not actual movements. In this study, we aim to characterize effort discounting during a decision between two alternative arm reaching movements. We asked if discounting minimizes movement-related variables that are linked to metabolic expenditure, to motor control costs, or to available sensory input. We tested which effort-related variables of an effortful movement were minimized by human subjects, comparing physical work, force level, impulse (force x duration) and other parameters. We tested for discounting-related movement parameters using a two-alternative forced-choice paradigm in which subjects had to choose between pairs of movements.

Movements were either of different durations, or of different amplitudes. Between trials we varied the friction-like resistive force against which each movement had to be performed with a robot manipulandum. During each trial, subjects experienced both of the alternative movements before expressing their choice by repeating the favored movement. This design allowed us to construct iso-effort curves, representing the force levels at which movements of different amplitudes or durations were deemed equivalently effortful. These iso-effort curves show that subjects are not sensitive to movement amplitudes, but base their choices on a non-linear combination of force and duration, even when temporal discounting was controlled for. We estimated this discounting as the product of duration by squared force. Moreover, subjects were sensitive to biomechanical factors, as arm flexions were preferred to arm extensions. Last, despite the variations in task performance between movements, the subjects did not systematically choose the reaches that had a higher chance of success. Our results show that humans mainly discount effort as a function of the duration of the movement and the force with which it is executed, which can be seen as a coarse approximation of muscle energy expenditure.

Disclosures: **P.D. Morel:** None. **P. Ulbrich:** None. **A. Gail:** None.

Poster

805. Reach Control: Selection and Strategy

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Topic: D.17. Voluntary Movements

Support: Australian Research Council (FT120100391)

Title: Humans learn to compensate for altered mechanical efficiency of one limb, but fail to optimise force sharing between limbs

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[2]Univ. of Queensland, Sch. of Biomed. Sciences, Lab. of Motor Control and Pain Resear, [3]CCRE Spine, Sch. of Hlth. and Rehabil. Sciences, The Univ. of Queensland, Brisbane, Au, [4]Ctr. for Sensorimotor Neuroscience, Sch. of Human Movement Studies, The Univ. of Queensland, [1]The Univ. of Queensland, Brisbane, Australia

Abstract: Although humans appear to use motor patterns which minimise intuited movement costs such as effort or variability, it is yet to be determined how this behaviour arises. Our previous work (de Rugy et al, J Neurosci 32:7384-7391, 2012) shows that subjects fail to optimise coordination between muscles in response to real or virtual changes in wrist

biomechanics, which suggests that the nervous system favours habitual, rather than optimal, coordination. Here we tested responses to virtual muscle efficiency changes in a bimanual force sharing task, to circumvent the criticism that the CNS might be insufficiently flexible to dramatically alter coordination patterns among muscles acting at a single joint. In the bimanual task, subjects can flexibly produce all possible force combination ratios if instructed, so any departure from optimal behaviour cannot be attributed to inflexibility within the neural control system. Subjects exerted both unimanual and bimanual radial deviation forces in the sagittal plane to reach circular targets, in one of three conditions; an effort-focused condition (n = 10, 4 males) with force targets at 48-64% of MVC and target radius equal to 40% of the target amplitude, an error-focused condition (n = 9, 5 males) with targets at 24-32% of MVC and target radius equal to 4% of amplitude, and an intermediate condition (n = 11, 7 males) with targets at 24-32% of MVC and radius equal to 15% of target amplitude. Each experiment consisted of five blocks of 60 trials, and in the middle three blocks, the efficiency (ratio of force to cursor movement) of the right arm was doubled. When we withheld visual feedback in 25% of trials, subjects proved able to accurately acquire both bimanual and unimanual targets, indicating that they implicitly detected and localised the imposed efficiency change, despite receiving no explicit instruction. Post-experiment questioning confirmed that they remained consciously naïve to the gain change. Critically, in all conditions, subjects responded in bimanual trials to the change in movement costs either by increasing the force output of the weaker wrist, or by displaying no significant change in force sharing. Although these strategies achieved the task goal, they are inconsistent with predictions from optimal control theory that the stronger hand should be favoured in order to minimise the total force produced. Thus, the CNS fails to optimise movement output on a timescale over which it successfully adapts performance in response to changed movement costs, even when the system has ample flexibility to produce the required coordination.

Disclosures: **M. Routson:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Australian Research Council (FT120100391). **K. Tucker:** None. **F. Hug:** None. **T.J. Carroll:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Australian Research Council (FT120100391).

Poster

805. Reach Control: Selection and Strategy

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Sloan Research Fellowship

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Title: A surprising lack a chunk-based learning in an implicit serial reaction time task

Authors: *M. A. SMITH[1], A. E. BRENNAN[1], D. PRESS[2];
[1]Sch. Engin., Harvard Univ., Cambridge, MA; [2]Dept. of Neurol., Beth Israel Deaconess Med. Ctr., Boston, MA

Abstract: Chunking refers to grouping components of a learning objective into small pieces, then learning the pieces separately. In memory tasks, chunking usually means grouping related items or ideas together to be recalled as a unit rather than as individual items. In this context, it has been shown to increase the effectiveness of capacity-limited working memory. In motor sequence learning, chunking usually refers to learning small subsequences before piecing them together. For example, one strategy for learning a piano piece would be to practice different phrases separately before playing the entire piece. Although chunking is generally thought to be a key component of implicit motor sequence learning, there is little direct experimental support. To examine chunk-based learning, we used a serial reaction time task in which subjects reacted to a cue as quickly as possible by pressing the corresponding key. With practice, subjects continually improved reaction times for an embedded repeating 12-item sequence, which they were unaware of, compared to trials presented in random order. Since the chunked subsequences should differ across individuals, we examined individual performance of the sequence using residual reaction times (RRTs) - computed as the average reaction time for each subject for each sequence element relative to the population average. We found clear evidence that most subjects consistently excelled at different sequence elements, and so we examined whether these differences were consistent with chunking. We examined three key predictions of chunking: (1) since the fastest RRT trials are likely part of a chunk, their neighbors are also likely part of a chunk and should therefore be faster than average; (2) since trials within a chunk have grouped improvement, there should be higher autocorrelation in the RRTs than in random noise . For both predictions, we found the data to be not significantly different from a no-chunking simulation with random noise RRTs, but strikingly different from simulations with chunking in which the chunk trials were just 30ms faster than non-chunk trials, with chunk lengths of 3-5 trials. Similar results were obtained for either 1 or 2 chunks in the sequence. Our findings show chunked improvements of just 30ms or more to be uncommon in serial reaction time learning. While we cannot reject chunking for improvements <30ms, models with sub-30ms effects could explain at

most 16% of the variance in RRTs, and are therefore unable to account for a substantial component of the learning behavior.

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Poster

805. Reach Control: Selection and Strategy

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Topic: D.17. Voluntary Movements

Support: NSF SES 1230933

NSF SES 1352632

Title: Reward expectation increases reach vigor

Authors: ***A. A. AHMED**[1], A. NIKOOYAN[1], E. SUMMERSIDE[1], R. SHADMEHR[2]; [1]Integrative Physiol., Univ. Colorado, Boulder, CO; [2]Biomed. Engin., Johns Hopkins Univ., Baltimore, MD

Abstract: Selecting which movement to perform may be represented as an economic decision in which the expected reward is offset by the cost of the movement itself. A critical prediction of this hypothesis is that we will move faster towards more rewarding goals. Indeed studies have demonstrated, in both humans and other animals, that the vigor of saccades is greater when the target of the movement is paired with reward, than for non-rewarding targets. Here, we asked whether the vigor of reaching movements is also modulated by the expected reward. Subjects (N=14) made reaching movements while seated and grasped the handle of a robotic manipulandum. They used the manipulandum to control a cursor that was displayed on a screen mounted in front of them. The experiment consisted of making out-and-back reaching movements from a central home circle to one of four targets displayed on the perimeter of a 10cm invisible circle, centered at the home circle. The targets appeared at 45, 135, 225, and 315 degrees in pseudorandom order. Subjects were instructed to reach to the target at a self-selected velocity. To prevent corrective movements, the cursor was not visible on the outward movement away from the home circle. Importantly, subjects were not penalized for accuracy. In the first 100 trials, no targets were rewarded (baseline). The target would simply change color from orange to gray once the circle's perimeter was crossed. The following four blocks of 100 trials were REWARD blocks. In each block, one of the targets was rewarded once the perimeter was

crossed by creating a visual onscreen ‘explosion’, which was accompanied by a pleasant ‘beep’. The rewarded target did not change within each block and the order was randomized across subjects. The other targets in that block were not rewarded. To test whether reward increased movement vigor, we compared the average outward peak velocity to rewarded targets (R) with the average peak velocity to non-rewarded targets (NR) in the four REWARD blocks. We also compared movement duration, reaction time, movement extent and accuracy in a similar manner. We observed that peak velocity and movement extent were significantly greater towards the rewarded targets, compared with the non-rewarded targets ($P < 0.05$). Movement duration, and reaction time were also shorter towards the rewarded targets compared with the non-rewarded targets ($P < 0.05$). There was no significant effect of reward on accuracy. Therefore, people reach faster, further, and sooner toward stimuli that promise greater reward, highlighting a possible general role for reward in modulating movement vigor.

Disclosures: A.A. Ahmed: None. **A. Nikooyan:** None. **E. Summerside:** None. **R. Shadmehr:** None.

Poster

805. Reach Control: Selection and Strategy

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Topic: D.17. Voluntary Movements

Title: Measuring proprioception and spatial-motor coordination in children with somatodyspraxia

Authors: *V. W. CHU, K. KRISHNAN;
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Abstract: Deficits in sensory processing, particularly in proprioception, can severely impact a child’s ability to learn new skills, presenting as dyspraxia and affecting activities of daily living. Traditionally, assessments of sensory processing and proprioception abilities have been primarily clinically and behaviorally based, focusing on problematic behavioral outcomes (Lane & Schaaf, 2010). More work is needed in the development of accurate assessments for proprioceptive deficits. The purpose of this study is to explore the use of a computer tablet to measure proprioceptive capabilities in the upper extremities. We postulate that deficits in proprioception leads to observable difficulties in spatial-motor coordination in children with dyspraxia. We recruited 5 children with somatodyspraxia (4 to 10 yo, mean: 7.6 yo) and 5 age-matched typically developing children (5 to 10 yo, mean: 7.5 yo) from the University of Illinois Hospital

and Health System and surrounding area. Informed assent and consent was obtained from the participants and their parents. We assessed spatial-motor coordination using a figure copying activity on a computer tablet in 2 conditions: active-active, passive-active. In the active-active condition, children were asked to copied shapes with vision of their hands. Immediately following the first attempt, the children were asked to repeat the figure without vision of their hand. In the passive-active condition, children's hands were moved passively to trace a figure, without vision of their hands. The children were then asked to draw the figure based on what they felt, without vision of their hands. Children were asked also to verbally identify the figure that they drew. The performance in the two conditions provides insights into the contribution of proprioception in spatial-motor coordination. Proprioception was further assessed through joint position sense of the elbow and wrist joint. Children in the dyspraxia group had more difficulty with drawing a figure with or without vision, showing larger geometrical and spatial errors. Children with dyspraxia also had more difficulty identifying the figures that were passively drawn. In the proprioception test, children in the dyspraxia group had more errors in the single joint angle matching tasks. The methods described in this study allow us to quantitatively characterize proprioceptive deficits. This study explores the relationship between quantitative direct measures of proprioception and measures of spatial-motor coordination through a drawing task, which could be done in a clinic setting, providing clinicians with another tool to improve clinical evaluation of somatodyspraxia.

Disclosures: V.W. Chu: None. **K. Krishnan:** None.

Poster

805. Reach Control: Selection and Strategy

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Topic: D.17. Voluntary Movements

Support: Canada Research Chair Program

Faculty of Health, York University

Title: Cortical mechanisms underlying the integration of transport and grip components for grasping

Authors: *A. LE[1,2], S. MONACO[3], Y. CHEN[2], J. D. CRAWFORD[2];
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Abstract: Grasping is a fundamental skill that we need to interact with our environment. Research on this topic to date has largely emphasized the independence of the reach (transport) and manual grasp (grip) components of this behavior. However, to successfully grasp an object, the transport of the arm and hand must be closely coordinated with the grip. It is currently unknown how these components are integrated by the human brain to produce reach-grasp coordination. To investigate this, we used slow event-related fMRI to examine the neural circuits involved in the integration of reach direction and grasp orientation. Participants performed a cue-separation task in which they received (a) visual information about the object location and (b) auditory information about the grasp orientation, in two successive phases. In one condition, participants were first cued about the location of the object (left or right), and then after an 8 second delay, they were cued about the grasp orientation (horizontal or vertical), followed by another 8 second delay, after which the participants grasped the object. In another condition, the cues were given in the reverse order. We predicted that brain areas associated with reach-grasp integration would respond more strongly during the second delay compared to the first delay, because of the added integrative processes of visual information about the object's location into action planning. We performed voxelwise analyses and found evidence for such integration in the anterior intraparietal sulcus (aIPS), ventral premotor cortex (PMv), and primary motor area (M1) in the left hemisphere. The results suggest that the integration of reach with grasp orientation does not occur in separate, special-purpose brain areas, but rather within the well-known anterior dorsolateral grasp-network. These results are potentially significant in the clinic for correlating locations of brain damage with symptoms of reach-grasp coordination and for the design of rehabilitation strategies for such patients.

Disclosures: **A. Le:** None. **S. Monaco:** None. **Y. Chen:** None. **J.D. Crawford:** None.

Poster

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Program#/Poster#: 805.25/U34

Topic: D.17. Voluntary Movements

Title: The involvement of the wrist in hand preshaping during grasping

Authors: *L. F. SCHETTINO, S. TROUT, M. BARRETT, N. STEINBERG;
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Abstract: During a reach-to-grasp movement, the shape of the hand changes based on target object shape (Santello & Soechting, 1998; Schettino et al., 2003), center of mass location (Lukos

et al., 2007) and behavioral goal (Craje et al., 2011). Coordination patterns of finger position and joint angle during a grasping movement have been previously described. However, the involvement of the wrist joint in hand preshaping and coordination has received less attention. Our study was designed to determine the extent to which wrist joint extension and deviation affect hand preshaping during a grasping task. Ten right-handed subjects grasped two objects of different shapes in two different orientations in two different placements: flat on a table or supported in mid-air. The two different object orientations required the ulnar deviation of the wrist to produce an effective grasp. Similarly, compared to table placement, the mid-air placement required an extension of the wrist to grasp appropriately. Electromagnetic tracking sensors (SR: 240 Hz) were positioned on the subjects' fingers and on the dorsum of the hand. We used principal component analysis to analyze the developing handshapes as the movement unfolded at 10% relative time increments in order to determine the effects of wrist deviation and extension on hand preshaping. Our results showed that the first and second principal components explained over 80% of the total variance. The first component identified the effects of wrist deviation on hand preshaping while the second component was mostly affected by object shape. Interestingly, wrist extension did not result in detectable handshape differences.

Disclosures: **L.F. Schettino:** None. **S. Trout:** None. **M. Barrett:** None. **N. Steinberg:** None.

Poster

806. Motor Learning: Behavior

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Topic: D.17. Voluntary Movements

Support: DFG HA 6861/2-1

NSERC

Title: The contributions of perception and prediction to changes in hand localization after visuomotor adaptation

Authors: ***B. M. 'T HART**, H. CLAYTON, D. Y. P. HENRIQUES;
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Abstract: Motor learning presumably results in changes in predictions about the sensory outcome of planned actions, which would in turn affect state estimates of limb position. To understand motor learning, access to these predictions - or how they change - would be desirable.

Several studies have asked participants to localize their invisible, trained hand with their untrained hand as a measure of state estimate that should be sensitive to changes in predictions of the sensory outcome of actions as a result of motor adaptation (Izawa & Shadmehr, 2012; Synofzik et al., 2008). However, estimates of limb position also rely on actually perceived limb position and although vision was removed in these studies, felt hand position - proprioception - was still available. Since our lab has shown that felt hand position is also recalibrated as a result of motor adaptation, it is likely that changes in localization result from changes in perceived hand position. We tested this by having 21 participants train with both aligned visual feedback and with a gradually introduced visuomotor rotation of 30°. Subsequently, they estimated the location of their hidden, trained hand with their seen, untrained hand after a movement. Crucially, this movement could be a passive hand displacement, controlled by a robot, or it could be actively generated by the participant. In self-generated movements, there is an efference copy, allowing predictions about upcoming sensory feedback, whereas passive hand displacements prevent such predictions. Both types of hand movement are sensitive to changes in perceived hand position though. Hence any changes in localization following passive displacement should be attributed to changes in perceived hand position. We found a significant change in hand localization following training with rotated feedback, both when the hand was placed passively as well as actively. The magnitude of the change when indicating the location of the unseen hand after it was displaced by the robot was over two thirds of the change measured with participants' self-generated hand movements. Consequently, predicted sensory consequences of movements are not solely responsible for changes in localizing the adapted hand after training with a perturbation. Instead, a large proportion of the changes recorded with localization appear to stem from changes in perceived hand position. Our results indicate the inherent problems with isolating predicted sensory consequences. Our results also stress the considerable contribution of felt limb position, or proprioception, to state estimates used in motor performance.

Disclosures: **B.M. 't Hart:** None. **H. Clayton:** None. **D.Y.P. Henriques:** None.

Poster

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Topic: D.17. Voluntary Movements

Support: National Institute of Child Health and Human Development R01 HD075740

Le Fonds Québecois de la Recherche sur la Nature et les Technologies (Quebec)

Title: Generalization of reinforcement based motor skill learning

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Abstract: A large literature has assessed generalization of learning in the context of sensorimotor adaptation tasks, mostly showing that generalization is limited. Little is known about the characteristics of generalization when one learns a novel motor skill, for which initially there is limited sensory error information available and instead learning is heavily based on exploration and reinforcement. We developed an experimental analogue of this process. Participants make reaching movements without visual feedback of the hand to an unseen target location embedded within a visually presented bar that runs the width of the display screen. Movements that successfully end within the target zone are indicated by a reward signal, whereas no error information is provided for unsuccessful ones. Before and after the training, participants are tested for their ability to reach to target bars at 7 different orientations in the workspace: the trained orientation and 6 non-trained orientations, 3 on each side of the trained location and progressively farther away from it. We measure movement accuracy as the absolute error from a straight line joining start and unseen target position at movement peak velocity. Movement bias is quantified as the signed error from the same trajectory. Results show that participants significantly reduce movement error and eliminate the initial bias for the trained location. For the non-trained locations, similar to previous studies on generalization, no changes are seen for movement directions beyond 30 degrees from the trained target. However, for the closer targets, a pattern of generalization is observed that differs from the gradient commonly observed in motor adaptation studies. At all locations, movement bias changed in the same direction observed for the trained location, thus resulting in either decreased or increased bias depending on baseline scores. Consistent with the change in bias, movement accuracy increased or showed a tendency to decrease, respectively. The results are compatible with a view of generalization involving a global re-orientation of the representation of the workspace around the trained target. The characteristics of generalization in these early stages of motor learning differ from what has been previously described for motor adaptation in the shape of the generalization function, but is similarly limited in extent.

Disclosures: **N.F. Bernardi:** None. **M. Clarke:** None. **D.J. Ostry:** None.

Poster

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Topic: D.17. Voluntary Movements

Support: NIH Grant GM007057

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NIH Grant HD040289

Title: Is implicit learning overestimated during an explicit aiming task?

Authors: *K. DAY[1], R. ROEMMICH[1], A. BASTIAN[1,2];
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Abstract: The mechanisms underlying motor adaptation are commonly studied using visuomotor rotation paradigms. Recent studies suggest that visuomotor learning involves two components: an implicit adaptation process driven by sensory-prediction error and an explicit process driven by target error. The implicit component has been derived previously by simply subtracting the subject's verbally reported aim (i.e., explicit component) from the target error on each trial. As this method relies upon a cognitive measure (reported aim) to explain a motor phenomenon (building of a forward model), whether this subtraction method accurately estimates the implicit learning process remains debatable. Here, we use direct and indirect measurements of implicit learning to understand how these learning processes interact during motor adaptation. Participants performed a visuomotor rotation paradigm (45 degree, clockwise rotation) consisting of 5 blocks—48 no rotation/no reported strategy trials, 8 no rotation/reported strategy trials, 320 rotation/reported strategy trials, 40 aftereffect trials, and 40 washout trials. Participants were placed in either an 8-target group with the target presented pseudorandomly at increments of 45 degrees or a 1-target group with the target always presented directly ahead of the starting position. Importantly, we also collected one catch trial every forty trials during the rotation block as a direct measure of the implicit learning process. During the catch trials, feedback was withheld and participants were instructed to aim directly at the target. Following the rotation block, participants were exposed to similar trials without feedback to evaluate aftereffects. Thus, we quantified the implicit process using two methods: by calculating the error in each catch trial over the course of adaptation (direct) and using the previously established subtraction method (indirect). We observed that the implicit process was consistently smaller when quantified by the direct method versus the indirect method. This finding prompted the obvious question—which result is more accurate? When quantified using the direct method, the implicit process was continuous with the motor output of the first aftereffect trial whereas the indirect method led to an implicit process that dropped sharply between the rotation and aftereffects blocks. These results suggest that the implicit component of learning can be assayed directly to provide additional insight into the interaction between the implicit building of a forward model and explicit aiming adjustments that we observe during motor adaptation.

Disclosures: K. Day: None. **R. Roemmich:** None. **A. Bastian:** None.

Poster

806. Motor Learning: Behavior

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Topic: D.17. Voluntary Movements

Support: European Research Council, Advanced Grant no. 291339

Title: Quantifying performance and neuromuscular admittance during manual tracking of a visual target

Authors: *T. SOLIS-ESCALANTE[1], R. VAN DER VLIET[2], Y. YANG[1], A. C. SCHOUTEN[1], F. C. T. VAN DER HELM[1];
[1]Mechanical Engin., Delft Univ. of Technol., Delft, Netherlands; [2]Erasmus MC, Rotterdam, Netherlands

Abstract: Current neurorehabilitation can partially restore lost motor skills after brain injury (e.g. stroke). Understanding the mechanisms of motor skill learning could improve post-stroke rehabilitation. Practicing how to accurately execute a movement in the presence of (force) disturbances may offer a controllable scenario to evaluate skill learning. The goal of this work is to determine whether skill learning can be assessed when manually tracking a visual target in the presence of force disturbances, and whether the neuromuscular admittance of the forearm changes through the learning process. The neuromuscular admittance describes the dynamic relation between an external force and limb position, depending on visco-elasticity due to muscle (co)contraction and afferent feedback. Healthy volunteers (n = 7, right handed) practiced controlling a cursor using a robotic manipulator with movements of their right wrist. Their task was to track a moving target as accurately as possible (tracking behavior), while force disturbances were applied to the manipulator (disturbance behavior). The target movement (MS1) and the force disturbance (MS2) were designed as sums-of-sinusoids with mutually exclusive frequency components: MS1 contained 7 frequencies between 0.2 and 2.6 Hz, whereas MS2 contained 22 frequencies between 0.8 and 20 Hz. There were three training sessions in consecutive days. A training session consisted of 6 blocks of 15 trials (20 s), yielding 270 trials in total. Task performance was shown at the end of each trial. A skill score combined the time delay between the target and cursor (TAU), and mean squared error (MSE) between both trajectories. The score was normalized with the average performance from the first block. One participant was unable to conduct the task (excluded for analysis). The neuromuscular admittance was quantified with a Fourier-based spectral analysis. The admittance from each block was expressed as a frequency response function using the 5 trials with the best

performance, and validated with the mean variance-accounted-for (VAF) in a leave-one-out procedure. Tracking behavior: There was significant performance increase between the first two training days (t-test, $p = 0.004$), but not between the second and the third day ($p = 0.741$). Performance increase was related to reduction of TAU and stable MSE. Disturbance behavior: The average admittance did not change across blocks. However, the average VAF was 61%, suggesting that behavior among validation trials is not homogeneous. Thus the link between tracking behavior and disturbance behavior should be treated as time-variant.

Disclosures: **T. Solis-Escalante:** None. **R. van der Vliet:** None. **Y. Yang:** None. **A.C. Schouten:** None. **F.C.T. van der Helm:** None.

Poster

806. Motor Learning: Behavior

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Topic: D.17. Voluntary Movements

Support: NSF Grant 1200830

Title: Learning vs. minding: how subjective costs mask motor learning

Authors: ***C. M. HEALY**[1], A. A. AHMED[1], M. BERNIKER[2];
[1]Univ. of Colorado, Boulder, CO; [2]Univ. of Illinois, Chicago, IL

Abstract: In trying to understand how people adapt their reaches, it is generally assumed that the amount of error is inversely proportional to how much a subject has learned. Sensibly then, smaller errors should indicate greater learning. This interpretation has helped advance our understanding of motor control in many ways. Interestingly, this idea implies that how much and how fast one learns varies with age, since older adults produce relatively larger errors. This apparent lack of learning relies on the assumption that a subject's objective is to exactly cancel the learned disturbance. Yet different objectives could result in varying errors but with the same amount of learning. We demonstrate how a controller that balances the trade-offs between subjective costs and error can produce equivalent control laws_and thus, trajectories_suggesting that different objectives can mask the true amount that a subject has adapted. To further test this hypothesis, we analyzed differences in how young and older adults adapted their reaches in a velocity-dependent curl field. We use an optimal control framework to produce theoretical trajectories to describe these reaches. While an internal model of the reaching dynamics directly reflects the true amount of adaption, metrics such as maximum perpendicular error, maximum

perpendicular force and force-velocity relationships within channel trials (adaptation index) can only infer this quantity. By comparing the internal model to the measured metrics of adaptation, we can determine how well these metrics capture the true adaptation process. Using channel trials, young adults were found to compensate for 84% of the curl field, while older adults compensated for only 65%. Using our model, trajectories with an internal estimate of 75% of the curl field gain were statistically indistinguishable from younger adult data, while trajectories with 70-75% were statistically indistinguishable from older adult data. These results call into question whether or not older adults actually adapt less than younger adults, or if they merely compensate less than young adults. Additionally, these results refine widely held assumptions regarding how to probe motor learning and which error metrics are appropriate. With further investigation into these topics, we may better quantify the learning process.

Disclosures: C.M. Healy: None. **A.A. Ahmed:** None. **M. Berniker:** None.

Poster

806. Motor Learning: Behavior

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Topic: D.17. Voluntary Movements

Support: McKnight Scholar Award

Sloan Research Fellowship

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Title: Identification of a motor memory that is fully retained 24h after training

Authors: *A. E. BRENNAN, M. A. SMITH;
Harvard Univ., Cambridge, MA

Abstract: Long-term retention (LTR) is a fundamental goal of most motor training: from learning the violin to throwing a Frisbee, the intention of a practice session is generally to improve the skill for future recall rather than to perform better during the practice session itself. In fact, we have previously shown that achieving higher performance during a practice session can be experimentally dissociated from higher LTR. Here, we examine the mechanism linking training to LTR measured 24 hours later. . We previously decomposed learning into a temporally-labile fast process, which learns quickly but also forgets quickly, and a temporally-stable slow process, which learns more slowly but also retains better. We have also previously

observed LTR to be a fixed fraction of the slow process. However, this observation could arise in two distinct ways: (1) slow process adaptation could be partially consolidated so that only a fraction remains 24h later; or (2) slow process adaptation could be composed of distinct components, one of which is retained over 24h and one of which is not. These two possibilities would lead to different strategies for optimizing LTR from a training session, with a focus on improving consolidation yield in the first case versus on directing training to specifically target LTR-stable learning in the second case. . Here we were motivated by the observation that repeated movements without error appears to cause slow process adaptation to decay substantially but not completely. We wondered whether this corresponded to distinct parts of the slow process that had different retention properties. We therefore compared the 24h retention of a 200-trial force-field training session that either was or was not followed by 500-trial error clamp trials. . In the group without error clamp exposure, 61±7% of slow process adaptation was retained 24h later. In contrast, only 30% of slow process adaptation remained after error clamp exposure, but 116±22% of this remaining adaptation was retained 24h later, corresponding to full retention. The sharp difference in 24h retention ($p = 0.02$) suggests slow process adaptation is composed of a long-term stable component of motor memory that is completely retained after 24h and a long-term unstable component that decays with repeated error clamp trials. . Future work will investigate why error clamp exposure reduced the total learning retained after 24h: whether the long-term stable component decays partially with error clamp trials, the long-term-unstable component is partially retained 24h later, or there is a 3rd component that is fully retained but decays with error-clamp trials.

Disclosures: **A.E. Brennan:** None. **M.A. Smith:** None.

Poster

806. Motor Learning: Behavior

Location: Hall A

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Program#/Poster#: 806.07/U41

Topic: D.17. Voluntary Movements

Title: Can flexibility of reaching movements be increased through training?

Authors: R. M. BONGERS[1], I. TUITERT[2,1], M. M. SCHOEMAKER[1], *L. J. MOUTON[1]; [1]Univ. of Groningen, Univ. Med. Ctr. Groningen, Groningen, Netherlands; [2]Aix-Marseille Université, Inst. des Sci. du Mouvement, Marseille, France

Abstract: The current study examined whether flexibility of a reaching movement can be increased through a variable practice intervention. Flexibility in motor behavior is defined as

accomplishing the same action goal with different joint coordination patterns. The question was whether practicing the use of a larger range of joint coordination patterns in an intervention resulted in more flexibility after the intervention. The pretest, on day 1, and the posttest, on day 3, consisted of 30 trials of 30cm reaching movement over an obstacle (height: 10cm, placed at one third of the movement distance). The intervention, on days 1 to 3, consisted of 200 reaching movements per day over one of 10 different obstacles (heights: 5-9cm and 11-15cm, steps of 1cm) in quasi-random order. The pretest, intervention and the posttest were analyzed with the UCM method. With the UCM method we partitioned variability in joint angles over repetitions of reaching movements in two types of variability: a) goal equivalent variability (GEV): variability in joint angles that does not affect the end-effector position, and b) non goal equivalent variability (NGEV): variability in joint angles that results in variability of the end-effector position. The ratio over GEV and NGEV implicates the flexibility of a movement. Results showed that during the intervention GEV was lower compared to the pre- and posttest while NGEV was higher. Comparison of pre- and posttest showed a decrease of both GEV and NGEV after the intervention, however flexibility (GEV/NGEV) did not change. This implies that over training joint angle variability becomes smaller while flexibility was maintained. This conclusion does not support our expectations because we aimed to increase flexibility through an increase of the joint angle ranges exploited during the intervention. Future studies will exploit whether the same effects are observed when a test task is used that is less overlearned.

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Poster

806. Motor Learning: Behavior

Location: Hall A

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Topic: D.17. Voluntary Movements

Support: Australian Research Council

Title: Visuomotor adaptation generalizes partially in head- or eye-centred coordinates

Authors: ***E. POH**[1], G. WALLIS[1], A. DE RUGY[2], S. RIEK[1], T. J. CARROLL[1];
[1]The Univ. of Queensland, St Lucia, Australia; [2]Univ. de Bordeaux, Bordeaux, France

Abstract: Humans can adapt to visual feedback that distorts the normal relationship between visual target direction and the direction of hand movement. This process called visuomotor

adaptation is thought to occur via a recalibration of the brain's spatial mapping between the visual environment and the issued motor command. How such maps generalize to untrained conditions may reflect the coordinate systems in which visuomotor remapping is represented We previously used an isometric wrist force aiming paradigm to assess the degree to which a new map between a visual target direction and isometric wrist force generalizes across different head roll angles (Poh et al, SfN 2013). When a 30° rotation of the visual feedback was introduced gradually, the generalization pattern was partially shifted (25%) relative to the degree of head roll, consistent with a representation that combines head/eye- and body-centred coordinate systems. However, because the experiment was performed in full lighting, salient cues drawn from the edges of the monitor provided allocentric information as to where the target is relative to the extrinsic world. This resulted in conflicting allocentric and eye/head-based information of target position at the generalization head posture, such that expression of generalization in head-centred coordinates is reduced. Here we examined if the shifts in the generalization pattern can be accentuated by aligning all visual information with respect to head orientation. To achieve this, subjects were trained in the dark and provided with allocentric cues in the form of a rectangular frame surrounding the stimulus that were congruent with the degree of head roll in each of the two postures. A 30 ° visuomotor rotation was imposed in steps of 0.5° for a single force direction (120 trials) with the head rolled either +30° or -30 from midline such that the training target was aligned with the sagittal axis of the head. Generalization was assessed without visual feedback to 13 targets, in a range of ±90° from the head-aligned target in each posture. We observed a 40.1% shift when head position was shifted to the generalization head position. This indicates that allocentric cues may marginally enhance the extent of head-centred generalization, and confirms that a representation of target direction in head- or gazed based coordinates does not fully account for generalization of isometric visuomotor rotation learning. These results add to evidence that multiple coordinate systems (eye, head object-centred) are involved in generalization of sensorimotor learning.

Disclosures: **E. Poh:** None. **G. Wallis:** None. **A. de Rugy:** None. **S. Riek:** None. **T.J. Carroll:** None.

Poster

806. Motor Learning: Behavior

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Topic: D.17. Voluntary Movements

Title: Spatial and attention abilities are more predictive of motor learning in younger adults compared to older adults

Authors: T. J. SHELAT[1], M. R. BROWN[1], V. MYRTHIL[2], *J. LANGAN[3];
[1]Rehabil. Sci., [2]Univ. at Buffalo, Buffalo, NY; [3]Rehabil. Sci., Univ. At Buffalo, Buffalo, NY

Abstract: BACKGROUND: Previous work has explored relationships between cognitive and motor performance. For example, proprioception using a joint matching paradigm has been shown to have a positive relationship to spatial working memory abilities. We aimed to further this line of research examining the relationship between motor learning and cognitive abilities such as spatial abilities and attention. OBJECTIVES: The purpose of this study was to: 1) Investigate the relationship between cognitive abilities (spatial memory and attention) and motor learning and 2) Compare these results between younger adults (YA) and older adults (OA). METHOD: Participants (YA=19; OA=24) completed a paper-based spatial assessment (card rotation task) and two computer-based assessments examining attention (reaction time) and motor control (a chase task using the computer mouse). Adding a motor control task allowed us to investigate if these cognitive abilities have similar associations across motor tasks. Subsequently, participants were asked to perform a motor learning task using a video game in which they adjusted their grip pressure to hit a sequence of six targets on a screen. To move to the next target, the pressure had to be maintained for 750 milliseconds. Targets for right and left hands were never the same. The pressure required to meet any given target never exceeded 21% of a participant's maximum strength. This sequence of six targets was repeated 60 times with each hand. We analyzed correlations between the end performance in which the participants performed the learned task bilaterally and the other assessments: spatial, attention and motor control. End performance was determined by the average amount of time to complete the six target sequence bilaterally in the last five trials of the session. RESULTS: OA did not show a significant relationship between end performance and the other assessments. However, YA did show a statistically significant correlation between end performance of the learned task and both spatial abilities and attention. Those who had a higher percentage correct in the spatial task, had lower times in completing the target sequence. Also, lower reaction times were associated with better end performance of the learned task. The correlation between end performance and motor control did not reach levels of statistical significance and only attention was related to performance of the motor control task, not spatial abilities. CONCLUSION: Spatial and attention abilities are associated with better end performance of a learned motor task in YA. This suggests cognitive abilities are used differently by YA compared to OA in learning a new motor task.

Disclosures: **T.J. Shelat:** None. **M.R. Brown:** None. **V. Myrthil:** None. **J. Langan:** None.

Poster

806. Motor Learning: Behavior

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Program#/Poster#: 806.10/V2

Topic: D.17. Voluntary Movements

Title: Adaptation to neural noise manipulation in voluntary movement control

Authors: *C. J. HASSON, O. GELINA, G. WOO;
Dept. of Physical Therapy, Movement and Rehabil. Sci., Northeastern Univ., Boston, MA

Abstract: Neural noise plays an important role in human movement control. It is known that neural control signal variability increases with amplitude (i.e. is signal-dependent), and motor variability induced by neural noise can be suppressed with antagonistic muscular co-activation. However, what remains unclear is how humans adapt to changes in neural noise, which can occur through various disease states and may accompany aging. To investigate this issue, we manipulated neural noise in ten healthy young adults, who used a myoelectric virtual arm to perform a goal-directed task. Neural noise was manipulated by adding or reducing the variability of the myoelectric signals driving the virtual arm. The task was to flex the virtual arm past a waypoint 45° away and return to the starting position with speed and accuracy. On one day subjects practiced the task for 4 blocks of 60 trials. The next day, subjects performed a series of isometric contractions at different effort levels to determine muscle-specific coefficients of variation (CV). Subject then practiced the task for 60 trials without manipulations. In the next 4 practice blocks, neural noise was increased and decreased in alternating blocks without subjects' knowledge. The order of the manipulation blocks was not randomized so noise adaptations across blocks could be assessed. Before each manipulation block of 45 trials, subjects performed 15 trials without manipulation. Neural noise was increased by adding noise to subjects' muscle activity signals to increase the CV by 100%. Noise was reduced by low-pass filtering the muscle activity signals, reducing the CV by 30%. Task performance was assessed by speed and accuracy, and antagonistic co-activation quantified by the overlap between biceps and triceps muscle activity linear envelopes. Task performance and co-activation with each noise manipulation was compared to the immediately preceding block of 15 non-manipulated trials. The results showed that initially, subjects responded to increased neural noise by increasing antagonistic co-activation, with speed and accuracy unchanged. With practice under increased noise, antagonistic co-activation decreased; speed and accuracy was maintained. In response to decreased neural noise, subjects initially decreased their antagonistic co-activation, moved slower, and were more accurate. However, with practice, performance became worse (i.e. slow and inaccurate), and antagonistic co-activation increased. These results suggest that humans can adapt to increased neural noise to maintain task performance without elevated antagonistic co-activation, and that decreasing neural noise is not necessarily beneficial.

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Poster

806. Motor Learning: Behavior

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Program#/Poster#: 806.11/V3

Topic: D.17. Voluntary Movements

Support: NIH Grant 106284

Title: Individual behavioral marker for identification of explicit awareness during sequential motor learning

Authors: ***R. LAWSON**, L. WHEATON;
Applied Physiol., Georgia Inst. of Technol., Atlanta, GA

Abstract: The learning of motor skills required for daily function in a rehabilitative setting often utilizes practice sessions involving multiple repetitions of the desired movements. While the value of simple repetition has been well established, it has been suggested that continued practice, in which explicit awareness of the movement pattern develops, can result in overlearning of that pattern, resulting in a reduced ability to generalize to new or more complex tasks. This study evaluated the potential for an individualized performance threshold to provide an indication of the development of explicit awareness during the learning of a serial reaction time task (SRTT). Subjects were exposed to varying levels of difficulty in the SRTT to examine the generalizability of the threshold. Results showed that subjects reaching performance below threshold indicated explicit awareness of sequence, while those failing to reach threshold were unable to repeat the sequence. These results suggest that a behavioral marker based on individual baseline performance may provide an accurate measure of when explicit awareness has developed.

Disclosures: **R. Lawson:** None. **L. Wheaton:** None.

Poster

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Topic: D.17. Voluntary Movements

Support: NIH Grant R01 HD065438

NSF Grant BCS 1031899

Title: Robust use-dependent learning in reaching movements without error or reward feedback

Authors: A. S. BAINS[1], *N. SCHWEIGHOFER[2];
[1]Neurosci., USC, Los Angeles, CA; [2]Univ. So California, Los Angeles, CA

Abstract: Previous work has suggested that repetition of a learned movement induces bias towards that movement when executing similar movements (Han et al 2008, Classen et al 1998, Diedrichsen et al 2010, Verstynen and Sabes 2011). Such use-dependent learning is thought be a slow process rooted in long-term potentiation in the motor cortex (Han et al 2008, Verstynen and Sabes 2011, Galea and Celnik 2009). Here, we test the hypotheses that use-dependent learning 1. has a slow time course and requires extensive training; 2. does not require feedback from the environment; and 3. is relatively resistant to time-based forgetting and to washout. Two subject groups took part in a two-day experiment. Subjects used a pen and tablet to reach to targets displayed on a horizontal screen which also acted to hide the subject's hand from view. Reaches were made without online feedback and trials were terminated once endpoint velocity fell below 25 mm/s. Group 1 was provided with endpoint error and score feedback after each trial, while Group 2 was shown only endpoint error on 20% of trials. Subjects trained by repeating 476 reaches in a single direction during Day 1 and another 238 at the beginning of Day 2. Over the first 100-200 trials during Day 1, both groups slowly developed a bias towards the repeated direction, measured using probe trials located 90° away from the repeated direction. This bias was still apparent at the beginning of Day 2, though it partially decayed by 3.0° ± 1.3° in Group 1 and 0.7° ± 0.5° in Group 2 from levels of 4.4° ± 1.6° and 2.7° ± 0.9° (mean ± SEM), respectively, at the end of Day 1. Additionally, after Day 2 training, the bias did not fully washout when subjects executed 203 reaches in random directions with error and score feedback available. Instead, the bias showed a partial washout of 1.7° ± 1.3° in Group 1 and 3.4° ± 1.3° in Group 2 from levels of 3.9° ± 1.4° and 5.2° ± 1.6° (mean ± SEM), respectively, at the end of Day 2 training. These results demonstrate that use-dependent learning 1. has a slow time course , 2. can be induced without error or reward (score) feedback, and 3. can last over 24 hours and is relatively robust to washout. Our results underline the potential importance of use-dependent learning as an independent mechanism of motor learning that may be harnessed in developing rehabilitation strategies after stroke or other motor impairments. In particular, use-dependent learning may lead to the "entrenchment" of compensatory movements in affected individuals: after such compensatory movements are "used" numerous times, it is difficult to re-train "normative movements", even with full feedback, as suggested by our washout paradigm.

Disclosures: **A.S. Bains:** None. **N. Schweighofer:** None.

Poster

806. Motor Learning: Behavior

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: D.17. Voluntary Movements

Support: NIH R01 Grant AG041878

McKnight Scholar Award

Sloan Research Fellowship

Title: Evidence for a rapidly evolving internal estimate of environmental variability in grip force control

Authors: ***A. M. HADJIOSIF**, M. A. SMITH;
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Abstract: Grip forces (GFs) are known to adapt to changes in expectations about environmental dynamics. However, we recently found that GFs are, in fact, 3-fold more sensitive to environmental variability than to the expected value of environmental dynamics (Hadjiosif & Smith, 2015). Here, we investigate the mechanism underlying this exquisite sensitivity. . The sensitivity of GF to environmental variability might arise from control directly based on an internal estimate of environmental variability. But it could also arise from asymmetric trial-to-trial adaptation that responds more strongly to unexpectedly high load forces than low ones, without requiring an internal estimate of environmental variability. Such an asymmetry would increase the GF levels associated with a given load force environment, because the GF decreases associated with unexpectedly small loads would be outweighed by GF increases associated with unexpectedly large loads. Critically, in higher variability environments where both very small and very large loads are more frequent, the effect of this asymmetry would increase, due to the increased gap between the small and large loads experienced, resulting in a systematic increase in GF control with load variability. . Here we use a trial-by-trial analysis of the changes in GF during exposure to a stochastic environment to distinguish between these possibilities. Asymmetric trial-by-trial adaptation that could support systematic variability-driven responses would predict larger increases than decreases in GF control following equal-amplitude increases vs decreases in load. However, GF adaptation driven by an internal estimate of environmental

variability would predict adaptive increases in GF control for *both* increases and decreases in load, with adaptive decreases in GF predicted only when expected loads are experienced. . We examined data from an experiment in which participants (N=51) used a precision grip to maintain grasp of a virtual object during 10cm point to point reaching movements. This object was perturbed by a viscous curl force field, whose strength, b, could randomly vary from one trial to the next, centered around zero. We found adaptive increases in GF control both when b>>0 *and* b<<0. These responses were both higher than when b=0 ($p < 0.001$ in both cases). In fact, the adaptive increases were essentially identical for b>>0 and b<<0 ($p = 0.44$). These data are at odds with asymmetric adaptation to high vs. low loads, but in line with an internal estimate of variability that evolves from one trial to the next, suggesting that motor system maintains a rapidly evolving internal estimate of the uncertainty about environmental dynamics.

Disclosures: **A.M. Hadjiosif:** None. **M.A. Smith:** None.

Poster

806. Motor Learning: Behavior

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Topic: D.17. Voluntary Movements

Support: NIH K08NS072183

Parkinson Disease Foundation Fellowship

Brain Research Foundation Seed Grant

Title: Evolution of limb kinematics during fine motor skill acquisition in rats

Authors: ***T. JOHN**[1], D. ELLENS[2], M. GAIDICA[2], S. PENG[3], D. LEVENTHAL[4];
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Abstract: The evolution of skilled movements has been studied using motion capture techniques in human subjects. To understand the neural underpinnings of motor skill acquisition, however, similar detailed kinematic analyses of fine animal movements is needed. Rodent skilled reaching, in which rats or mice are trained to reach for and grasp a food pellet, has been used for over two decades to study motor control. However, the task requires extensive human supervision to both run the task and analyze data. Furthermore, reaches are usually scored on a semi-quantitative scale, providing limited insight into how the reaching movement develops over time. We developed an apparatus that allows automated high throughput training and unsupervised

kinematic analysis of rat skilled reaching. Reaches early in the learning process were characterized by variability in paw trajectories, whether the animal successfully grasped a food pellet or not. As task proficiency improved, reaches took on a more stereotyped trajectory, again independent of reach success or failure. Importantly, variability in early reach trajectory was correlated with the degree to which reaching proficiency improved. This supports the notion that motor variability during task acquisition is important to explore potential movement strategies, so that the optimal strategy can ultimately be adopted. These results provide insight into how motor skills develop, and why some subjects become more successful than others.

Disclosures: **T. John:** None. **D. Ellens:** None. **M. Gaidica:** None. **S. Peng:** None. **D. Leventhal:** None.

Poster

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Program#/Poster#: 806.15/V7

Topic: D.17. Voluntary Movements

Support: NIH Grant NS084948

Title: Learning a visuomotor adaptation task without adaptation when the arm is visible

Authors: ***A. L. WONG**[1,3], J. A. TAYLOR[3], J. W. KRAKAUER[1,2];
[1]Neurol., [2]Neurosci., Johns Hopkins Univ. Sch. Med., Baltimore, MD; [3]Psychology, Princeton Univ., Princeton, NJ

Abstract: Under typical situations, introduction of a visuomotor rotation promotes implicit adaptation. We have previously demonstrated that, curiously, this adaptation persists despite providing subjects with complete awareness of the cursor manipulation (i.e., by informing subjects where they should aim to solve the rotation) and despite good task performance, leading to a counterintuitive gradual drift of the hand away from the target. That is, subjects know that the cursor is rotated relative to the true hand position and have proprioceptive information about their actual hand location. Nevertheless, they experience an unavoidable sensory-prediction error (i.e., derived by a forward model) between the expected outcome of the motor command sent to the hand and the observed movement of the cursor, which drives implicit adaptation. Here, we asked if additional visual information about true hand position, provided via direct vision of the limb, negates or can overcome sensory-prediction errors during a visuomotor rotation. Thus, vision, proprioception, and knowledge of the position of the hand are all congruent; solving the

rotation then becomes akin to playing a game. In this situation, subjects quickly recognize the presence of the cursor manipulation and formulate an aiming strategy to overcome the rotation. This aiming strategy is initially formulated independently for each target, but eventually becomes generalized into a single common strategy (e.g., "aim to a location clockwise from the target"). Furthermore, when subjects re-aim their hand, the amount of drift away from the target that they experience is dependent upon the certainty with which they can localize their hand position. Therefore, unlike knowledge or proprioception, vision of the hand can uniquely eliminate implicit adaptation in response to a hand-cursor visuomotor mismatch by providing direct evidence that there is no sensory-prediction error between the motor command sent to the hand and the observed consequences of that movement. This supports the argument that motor performance during adaptation tasks reflects the interaction between explicit strategy and implicit adaptation; thus, when implicit adaptation is impaired or suppressed, subjects can use explicit strategy to maintain good behavior.

Disclosures: **A.L. Wong:** None. **J.A. Taylor:** None. **J.W. Krakauer:** None.

Poster

806. Motor Learning: Behavior

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Program#/Poster#: 806.16/V8

Topic: D.17. Voluntary Movements

Title: Decision making during motor learning: investment in learning and reward optimization

Authors: *J. B. MOSKOWITZ[1], D. J. GALE[1], D. M. WOLPERT[2], J. P. GALLIVAN[1], J. R. FLANAGAN[1];
[1]Queen's Univ., Kingston, ON, Canada; [2]Univ. of Cambridge, Cambridge, United Kingdom

Abstract: In our daily lives we often must decide whether it is worth investing in learning a new skill (e.g., learning to play the guitar). This relies on weighting the costs/benefits associated with learning, the outcome probabilities, as well as prior knowledge. Successful evaluation depends on our ability to estimate our own learning parameters (e.g., our rate of learning and its variability) and the duration over which we have the opportunity to exploit this learning (e.g., a day or a lifetime). To our knowledge no work has explored the extent to which individuals can track their own learning and exploit this information to make optimal decisions related to future rewards. We examined this question by engaging subjects in a target-directed reaching task using a planar robotic manipulandum. After an initial practice phase, we applied a 45 degree visuomotor rotation to participants reaches. This adaptation block was short (30 trials) such that

participants did not fully adapt to the rotation. In a subsequent decision phase, subjects decided how many points they would like to receive for hitting and missing the target, respectively, for a future block of adaptation trials. Subjects made three separate point-assignments for future blocks that were short, medium, or long in trial length, respectively. At the end of the experiment subjects received a payout contingent on how many points they accrued during the study. Because learning curves are generally well-approximated by an exponential, we hypothesized that subjects should, in theory, be able to predict their future performance based on their performance during the short adaptation block and thus determine a point-assignment that should maximize their reward (i.e. optimal decision). On average, we found that participants selected point-assignments that were in the direction of optimal. That is, subjects chose riskier point-assignments (more points assigned to hitting than missing the target) the greater the length the future block was, suggesting that participants predicted their performance would improve over longer learning horizons. Furthermore, the results suggest that optimal point-assignments were easier for participants when their task performance was at the extremes (i.e., very poor or very good), but more difficult when their performance was mediocre. Taken together, these findings suggest that individuals can exploit information about their own learning in order to effectively guide decisions about future reward.

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Poster

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Topic: D.17. Voluntary Movements

Support: NWO-VICI: 453-11-001

NWO-VENI: 451-10-017

Title: Artificial vestibular cues enable dual motor adaptation

Authors: *L. P. SELEN, J. L. RUDOLPH, W. P. MEDENDORP;
Radboud Univ., Donders Inst. for Brain, Cognition and Behavio, Nijmegen, Netherlands

Abstract: When two opposing force field perturbations are presented sequentially, there is substantial interference between the associated motor memories. However, if contextual cues are

associated with each perturbation interference is reduced and subjects can readily adapt to both (see Howard et al., 2012, 2013). In a recent study we had subjects adapt to two opposite accelerating environments and showed that interference between motor memories is reduced (Sarwary et al., 2013). We attributed this reduction in interference to the availability of vestibular information that dissociated the two environments. Here we have a deeper look into this claim by investigating whether artificial vestibular signals can serve as a cue dissociating between two opposing perturbations. Subjects were asked to make two stage reaching movements on a robotic manipulandum. During the first stage of the reach a velocity dependent current was applied to the vestibular afferents through Galvanic Vestibular Stimulation (GVS). The sign of this current determined the direction of the curl-force field (CW or CCW) during the second stage of the reach. In a small fraction of trials the force field was replaced by an error-clamp. This allowed us to determine the force expression during the second stage of the movement induced by the GVS-cue in the first stage of the movement. Subjects do adapt to both force force fields as indicated by the increase in force expression in the error-clamps in opposite directions for the two vestibular cues. However, they never learn to fully compensate for the force fields, indicated by adaptation indices of about 0.5. We conclude that vestibular information does serve as a cue that enables adaptation to two opposing force environments at the same time. However, the arbitrary mapping between vestibular information and movement parameters probably prohibits full adaptation. Howard, I. S., Ingram, J. N., Franklin, D. W., & Wolpert, D. M. (2012). Gone in 0.6 seconds: the encoding of motor memories depends on recent sensorimotor states. The Journal of Neuroscience, 32(37), 12756-12768. Howard, I. S., Wolpert, D. M., & Franklin, D. W. (2013). The effect of contextual cues on the encoding of motor memories. Journal of neurophysiology, 109(10), 2632-2644. Sarwary, A. M., Selen, L. P., & Medendorp, W. P. (2013). Vestibular benefits to task savings in motor adaptation. Journal of neurophysiology, 110(6), 1269-1277.

Disclosures: **L.P. Selen:** None. **J.L. Rudolph:** None. **W.P. Medendorp:** None.

Poster

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Program#/Poster#: 806.18/V10

Topic: D.17. Voluntary Movements

Support: R01HD059783

Title: Training of the non-dominant arm leads to substantial and durable changes in performance

Authors: *A. DUNN[1], C. CHOPICK[1,2], R. SAINBURG[1,2];
[1]Kinesiology, Pennsylvania State Univ., State College, PA; [2]Neurol., Pennsylvania State Univ. Col. of Med., Hershey, PA

Abstract: Our previous studies have shown substantial asymmetries in motor performance between the dominant and non-dominant arms of healthy adults. Whereas the dominant arm appears specialized for predictive control associated with fast, efficient, and smooth trajectories, the non-dominant arm appears specialized for impedance control that leads to robustness in the face of unexpected perturbations. Functional tests of unilateral upper extremity performance, such as the Jebsen-Taylor Hand Function Test (JTHFT) show substantial performance asymmetries, with the dominant arm tending to perform a range of unimanual upper extremity activities roughly 20% faster than the non-dominant arm. Whether these performance asymmetries are amenable to modification through practice is not well-understood, although it is clear that individuals who have experienced a partial or complete dominant hand amputation largely switch their dominance over time, which is associated with increased activation of ipsilateral cortex (Philip BA, Frey SH (2014)). We now ask whether general training of predictive control using virtual reality, in combination with training of real-world coordination, can lead to significant improvements in speed and coordination of the non-dominant arm, as tested using the JTHFT. Our preliminary results suggest substantial and durable improvements in coordination and performance of the trained non-dominant arm. These results have substantial implications for dominance retraining in individuals with unilateral dominant-arm impairments, such as amputation and stroke.

Disclosures: A. Dunn: None. **C. Chopick:** None. **R. Sainburg:** None.

Poster

806. Motor Learning: Behavior

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Program#/Poster#: 806.19/V11

Topic: D.17. Voluntary Movements

Title: The role of attention in visuomotor and force field adaptation

Authors: *E.-M. REUTER[1,2], T. J. CARROLL[1], J. BEDNARK[2], R. CUNNINGTON[2,3];
[1]Sch. of Human Movement and Nutr. Sci., [2]Queensland Brain Inst., [3]Sch. of Psychology, Univ. of Queensland, Brisbane, Australia

Abstract: Attention is a crucial and well-studied aspect of cognition, but little is known about how it relates to processing and adaptation in the motor system. To learn a new visuomotor transformation visual attention is needed [1]. However, how attention changes throughout successful adaptation, and how motor adaptation affects spatial attention, remain open questions. In a series of experiments we tested groups of 20 healthy right-handed participants during visuomotor or force field adaptation. We used behavioural and/or EEG measures of attention and motor function to probe the effects of the sensorimotor perturbations. In Exp. 1 we investigated how visual attention changes throughout visuomotor adaptation to smaller (60°) and larger (120°) screen cursor rotations, using steady-state-visual-evoked-potentials (SSVEPs). In Exp. 2 we characterized the consequences for spatial attention of i) adaptation to persistent sensorimotor perturbations and ii) exposure to random perturbations that do not result in motor adaptation. The effects of the training were assessed pre-adaptation, 5-minute, and 30-minute post-adaptation via Visual Temporal Order Judgment and Visual Attention Dual-Task tests. Results of Exp. 1 showed that participants' performance improved over time in all conditions ($F(1,19) = 43.82$, $p < .001$, $\eta p^2 = .70$) and was influenced by the degree of rotation ($F(1,19) = 84.53$, $p < .001$, $\eta p^2 = .82$). We found that SSVEP EEG power, reflecting attention to the visual stimulus, decreased with improved performance for smaller rotation, but did not change with performance for larger rotation ($F(11,209) = 2.53$, $p = .04$, $\eta p^2 = .12$). The findings from Exp. 1 suggest that visual attention to the cursor decreased as performance increased, and that this is influenced by the difficulty of the new transformation. This might reflect a reduced reliance on visual attention for easier rotation, but continued reliance on attention to visual feedback of action for the more difficult rotation. Results of the ongoing Exp. 2 will indicate whether the interrelation between attention and motor adaptation is bi-directional. Reference: [1] Taylor, J. A., & Thoroughman, K. A. (2007). Divided attention impairs human motor adaptation but not feedback control, Journal of Neurophysiology, 98(1), 317-326.

Disclosures: **E. Reuter:** None. **T.J. Carroll:** None. **J. Bednark:** None. **R. Cunnington:** None.

Poster

806. Motor Learning: Behavior

Location: Hall A

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Topic: D.17. Voluntary Movements

Support: NSERC

Title: Time course of reach adaptation and proprioceptive recalibration during visuomotor learning

Authors: *J. E. RUTTLE[1], E. CRESSMAN[3], D. HENRIQUES[2];
[1]York Univ., Bolton, ON, Canada; [2]York Univ., Toronto, ON, Canada; [3]Univ. of Ottawa, Ottawa, ON, Canada

Abstract: Training to reach with rotated hand-cursor feedback, results in changes or adaptation of these hand movements during training, which continues to persist when the perturbation is removed (reach aftereffects), as well as changes in felt hand position, which we refer to as proprioceptive recalibration. The rate by which motor and proprioceptive changes arise throughout training is unknown. Here, we aim to determine the timescale of these changes and their relationship in order to gain insight into the processes that may be involved in learning. We measured reach aftereffects (no-cursor reaches) and perceived hand position after every 6 reach-training trials with a 30 rotated-cursor to 3 radially located targets. To assess proprioceptive recalibration, the right adapted hand was passively moved to one of the three target sites by a robot, and its perceived location was indicated by the left untrained hand. Participants trained with both a clockwise and a counter-clockwise cursor rotation in sessions a week apart to determine if the original training led to any retention or interference of these motor and sensory changes. Results suggest that both motor and proprioceptive recalibration occurred simultaneously and immediately after only 6 or 12 rotated-cursor training trials (13.08 & 4.50 respectively) and did not increase much or at all with further training. Moreover, there was no retention or interference present one week after training. This suggests that the implicit changes in both motor and sensory systems do not simply reflect changes in performance made with a cursor during training.

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Poster

806. Motor Learning: Behavior

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: D.17. Voluntary Movements

Title: Persistence of a neural representation following repeated adaptations to and repeated deadaptations from a novel visuomotor rotation

Authors: *S. BAO, J. WANG;
Univ. of Wisconsin Milwaukee, Milwaukee, WI

Abstract: When humans adapt their voluntary reaching movements to a systematic visuomotor perturbation, a neural representation that is associated with the novel condition, called an internal model, is thought to develop in the cerebellum. The adapted performance returns to baseline rapidly once the external perturbation is removed, and this procedure is called deadaptation. There are two opposite ideas about the mechanisms that underlie deadaptation: (1) the process of deadaptation results in the decay of motor memory that is associated with the internal model; and (2) the internal model is not decayed during this process, but rather allows the nervous system to have two distinct visuomotor transforms: the original visuomotor transform (related to baseline performance) and the novel visuomotor transform (related to adapted performance). In the present study, we attempted to test the two ideas by having individuals adapt to a novel visuomotor rotation and de-adapt from the rotation repeatedly. That is, our subjects first adapted to a visuomotor rotation; deadapted from the rotation; readapted to the rotation; deadapted from the rotation again; and readapted to the rotation once more. We hypothesized that if the internal model developed during initial adaptation was decayed following deadaptation, the extent of savings observed following the first deadaptation period would be similar to that following the second deadaptation period. Alternatively, we hypothesized that if the internal model remained intact following deadaptation, the extent of savings should be greater following the second deadaptation period than following the first deadaptation period. Results showed that the extent of savings observed during the second adaptation period was significantly greater than that observed during the first adaptation period, and the extent observed during the third adaptation period significantly greater than that observed during the second adaptation period. This finding indicates that the extent of savings continues to improve across multiple adaptation periods, which suggests that the internal model continues to be improved for better performance even after repeated deadaptation periods. This finding provides support to the idea that an internal model associated with a novel visuomotor transform is not decayed following a period of deadaptation, but rather allows the nervous system to contain both the original and a novel visuomotor transform simultaneously.

Disclosures: **S. Bao:** None. **J. Wang:** None.

Poster

806. Motor Learning: Behavior

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Topic: D.17. Voluntary Movements

Support: NSERC RGP 355931

Title: Exploring the value of practice in motor adaptation

Authors: *S. K. COLTMAN[1], L. E. BROWN[2];
[1]Psychology, Trent Univ. Dept. of Psychology, Peterborough, ON, Canada; [2]Trent Univ., Peterborough, ON, Canada

Abstract: Given that variability and performance have an inverse relationship, one question that we must address is, “What should we practice?” Practice provides an opportunity to learn to control highly variable movements as a novice with the goal being that precision will increase. We designed an experiment to examine the effect of constant versus variable practice, to assess which leads to greater precision when adapting a simple visually guided reaching movements. The experiment consisted of a 2-practice task (vary distance, vary direction) by 2-test task (vary direction, vary distance) between subjects design. Participants used their right hand to make simple point-to-point movements from a constant start position to one of three possible targets varying in direction or distance. All four groups practiced over 144 trials and tested over 144 trials, with focus for the analysis limited to the first 12 trials of testing to capture the effect practice condition on performance. Data was analysed from end-point variability, measured as the standard deviation of all end points, and movement time, measured as the time between initiation and cessation of movement. The results indicated that when the test task was to vary direction, greater precision was achieved when practice was to vary direction over distance, without compromising time. On the other hand, when the test task was to vary distance, there was no one task that was more beneficial to achieve greater precision, however, participants were able to significantly reduce time when practicing to vary distance over direction. So far, these results indicate that people should practice what they intend to perform. Subsequent analyses may reveal the role of functional and non-functional variability experienced during practice on test performance.

Disclosures: S.K. Coltman: None. **L.E. Brown:** None.

Poster

806. Motor Learning: Behavior

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Topic: D.17. Voluntary Movements

Title: Visuomotor adaptation and deadaptation with one arm result in savings during subsequent visuomotor adaptation with the other arm

Authors: *J. WANG, A. D'AMATO;
Dept Kinesiology, Univ. of Wisconsin, Milwaukee, WI

Abstract: Savings refers to a phenomenon in which individuals learn a motor task faster when exposed to the same learning condition again later. It has been suggested that savings is related to model-free, as compared with model-bsed, learning. However, savings is frequently observed following interlimb transfer of motor learning, which is thought to involve model-based, but not model-free, learning. In the present study, we explored the phenomenon of savings by examining how unlearning of a motor task with one arm would influence retention of the motor task with the same arm or with the other arm. A group of subjects experienced three experimental sessions: (1) adaptation to a 30-degree rotation during targeted reaching movements with the left arm; (2) deadaptation from the rotation with the left arm; and (3) readaptation to the rotation with the right arm. Another group of subjects experienced three sessions that were somewhat different: (1) adaptation to a 30-degree rotation with the left arm; (2) deadaptation from the rotation with the right arm; and (3) readaptation to the rotation with the left arm. Our general working hypothesis was that if the deadaptation caused the internal representation developed during initial training to be decayed, no savings would be observed during readaptation; and that the pattern of readaptation should be similar regardless of which arm was used during the deadaptation and readaptation sessions. Our results indicated that savings was observed in both subjects groups. Specifically, the former group showed savings during readaptation with the right arm following deadaptation with the left arm, which indicates that the deadaptation session did not cause the internal representation developed during initial training with the same arm to be decayed. The latter group showed savings during readaptation with the left arm following deadaptation with the right arm, which indicates that the deadaptation session did not cause the internal representation developed during initial training with the other arm to be decayed. Interestingly, the latter group also showed that the savings observed at the first few trials of the readaptation session was also associated with substantially low performance errors, which has not been observed in previous studies. Our findings collectively suggest that internal representations developed following visuomotor adaptation involve some aspects that are effector independent and other aspects that are effector dependent; and that the nature of savings can vary depending on whether it involves model-based learning, which is effector independent, or model-free learning, which is effector dependent.

Disclosures: J. Wang: None. **A. D'Amato:** None.

Poster

806. Motor Learning: Behavior

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Topic: D.17. Voluntary Movements

Support: JSPS KAKENHI 15K16366

JSPS KAKENHI 25871228

Title: Individual ability of motor imagery can determine the suitable attentional strategy under motor learning

Authors: *T. SAKURADA, M. HIRAI, E. WATANABE;
Jichi Med. Univ., Tochigi-Ken, Japan

Abstract: It has been shown that the motor learning performance can be affected by various cognitive factors such as directing attention and motor imagery ability. Most previous studies on motor learning have shown that directing the participants' attention externally, such as on the outcome of the body movement, can be more effective than directing their attention internally, such as on body movement itself. However, to our best knowledge, there are no findings regarding the effect of attention manipulation on motor learning performance, depending on individual's motor imagery ability. To clarify the individual differences, we first assessed individual motor imagery ability by using the Movement Imagery Questionnaire (MIQ-R) and classified participants into 2 groups on the basis of their scores. After that, the participants performed a simple motor learning task such as tracing a trajectory with visuomotor rotation. We introduced 3 experimental conditions (No Attentional Instruction condition, Internal Focus Attentional condition and External Focus Attentional condition). We defined the movement error as an index to evaluate the transition of motor performance and calculated the aftereffect size to evaluate the degree of motor learning in a wash-out trial. When the participants were required to direct their attention internally, the aftereffects of the motor learning task in the participants good at kinesthetic motor imagery were significantly higher than those of the participants good at visual motor imagery. Conversely, when the participants were required to direct their attention externally, the aftereffects of the participants good at visual motor imagery were significantly higher than those of the participants good at kinesthetic motor imagery. Furthermore, we found a significant correlation between the aftereffects of motor learning and the differential scores between visual and kinesthetic motor imagery abilities. These results suggest that individual intrinsic motor imagery ability can be related to the suitable attention strategy during a motor

learning task and the suitable attentional strategy under motor learning can be changed individually. Therefore, we should evaluate the individual differences to conduct motor learning tasks effectively such as using a simplified assessment for the purpose of applications in the sports and clinical fields. Our current findings can contribute to the first step in promoting tailor-made motor learning or rehabilitation programs.

Disclosures: **T. Sakurada:** None. **M. Hirai:** None. **E. Watanabe:** None.

Poster

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Topic: D.17. Voluntary Movements

Title: Development of collaborative strategies in physical human-human interaction

Authors: V. THEKKEDATH CHACKOCHAN, I. TAMAGNONE, *V. SANGUINETI; Univ. of Genoa, Genoa, Italy

Abstract: Physical human-human interaction plays an important role in our life experience and is the basis of many daily activities. If two partners have different goals, but a perfect knowledge of their respective goals and internal state, they may negotiate a joint strategy. However, it is unclear how the development of collaborative strategies is affected by lack of this information. To explore this we developed an interactive learning paradigm in which each subject sat in front of a computer screen and grasped the handle of a haptic interface. The two subjects could not see each other and were not allowed to talk. They were instructed to perform reaching movements with the same start and target position, but through different via-points. The haptic interfaces generated a force proportional to the difference of the two hand positions, so that the two subjects were mechanically connected. During movements the haptic interaction force was continuously displayed. At the end of each movement each subject received a 0-100 reward, calculated as a function of the minimum distance of their movement path from his/her own via-point and the average interaction force. Both subjects were instructed to aim at maximizing their score. They were also encouraged to maintain an approximately constant movement duration. We focused on two different scenarios: (i) visible via-point: each subject can see his own via-point but not his/her partner's. (ii) hidden via-point: no via-points were displayed, so that the score was the only information available to learn the movement and to develop a cooperation strategy. During a familiarization phase the interaction forces were turned off and each subject

performed on their own. In a later phase the two subjects were mechanically connected. They had the option to establish a collaboration - negotiating a path through both via-points, which would lead to a minimization of the interaction forces and a maximum score for both - or to ignore each other - each partner only focuses on their own via-point and on maximizing his/her own score. In the 'hidden' scenario, collaboration also affects the exploration of the space of the possible actions. In the analysis, we specifically focused on the temporal evolution of the trajectories (trial-by-trial variability), the scores and the magnitude of the interaction force. In both the visible and hidden scenarios, the subjects pair generally converged to a collaborative strategy, characterized by a minimization of the interaction forces. Lack of knowledge of partner's state (no visual feedback on interaction forces) reduced the trend toward collaboration.

Disclosures: V. Thekkedath Chackochan: None. **I. Tamagnone:** None. **V. Sanguineti:** None.

Poster

806. Motor Learning: Behavior

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 806.26/V18

Topic: D.17. Voluntary Movements

Support: McKnight Scholar Award

Sloan Research Fellowship

NIA (R01 AG041878)

Title: Investigating reward-based regulation of task-relevant motor variability in rats

Authors: *Y. R. MIYAMOTO, A. DHAWALE, M. A. SMITH, B. P. ÖLVECZKY; Harvard Univ., Cambridge, MA

Abstract: Motor variability can be equated with action exploration, a key ingredient of trial-and-error motor learning. The motor system is known to actively modulate its variability, consistent with the need for high-variability exploration when rapid learning is called for and low-variability exploitation when precision is desired for good performance (Tchernichovski et al. 2001; Kao et al. 2005; Wu et al. 2014; Pekny et al. 2015). Here we investigate how variability is regulated by reward in task-relevant dimensions, and the timescales involved. We studied 4 rats trained to press a small 2-d joystick downward with their paws, with a reward based on joystick trajectory angle. Animals were trained 2 to 4 times a day, in 30 minute sessions, amounting to 100,000+ trials over the course of a few months of training. To ensure that rats were continually

challenged to adapt motor output, we periodically shifted the rewarded joystick angle to a new value as the rats successfully adjusted to the target angle. The rats were able to perform this task proficiently; the rats' average error was 8 degrees from the target, much smaller than the size of typical target angle shifts, which ranged up to 50 degrees. When we examined the rats' behaviors following rewarded trials, we found that they systematically decreased joystick angle variability compared to pre-reward baseline trials ($p < 0.0001$), indicating a propensity to modulate task-relevant variability based on reward. To examine the relationship between reward and variability further, we administered reward randomly with different probabilities {0.1, 0.35, 0.7}, uncoupling it from performance in occasional blocks of 75 contiguous random-reward trials. We found that variability in press angles was larger on blocks with low reward rates and vice versa ($p < 0.0001$); in addition, we characterized the time-scale over which reward rates are integrated to influence variability, and found an exponential fit to the data to have an average time constant of 8.7 trials (99% CI: [6.5, 11.0]). In contrast, preliminary analysis suggests that the variability of task-irrelevant features, such as press velocity and path curvature, was not sensitive to these reward manipulations ($p = 0.26$, $p = 0.57$). Thus, the motor system may selectively modulate variability along the dimensions of motor output that are essential for the task, and do so by integrating reward information on a short, multiple-trial timescale.

Disclosures: Y.R. Miyamoto: None. **A. Dhawale:** None. **M.A. Smith:** None. **B.P. Ölveczky:** None.

Poster

806. Motor Learning: Behavior

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 806.27/V19

Topic: D.17. Voluntary Movements

Title: The training duration influences the magnitude of motor adaptation retention, but not the magnitude of savings following a 24-hour break

Authors: *K. P. NGUYEN[1,2], L. C. BRAY[2], L. ALHUSSEIN[2], E. A. HOSSEINI[3], W. M. JOINER[2];
[1]NIH, Bethesda, MD; [2]Dept. of Bioengineering, George Mason Univ., Fairfax, VA; [3]McGovern Inst. for Brain Res., MIT, Cambridge, MA

Abstract: There is growing understanding of the influence the training schedule exerts on different features of motor adaptation (retention, transfer, generalization and stability). Here, we were interested in the influence of training duration on the retention and savings (readaptation) of

a learned motor adaptation following a 24-hour break period. We trained subjects to make point-to-point reaching movements when perturbed by a position-dependent force-field in two experimental sessions completed over two consecutive days. The perturbation was suddenly applied, but the duration of training was either long (160 trials) or short (15 trials). Consistent with previous findings (Joiner and Smith, 2008) the training duration had a marked influence on the retention of adaptation on the second day of training with an approximate 74% decrease in retention with the shorter training duration. However, following the first trial of force-field exposure on the second day, the magnitude of savings was comparable for both training durations ($P = 0.51$). This was also true when the initial training on the first day was followed by a washout period ($P = 0.83$); the magnitude of savings was reduced by an equivalent amount for both training durations (> 20% in both cases). When we represented these results in a position/velocity gain-space (the amount of the observed temporal force pattern associated with limb position and velocity) there were differences in the orientation of the respective gain-space learning trajectories. In general, the initial trajectory for learning on the second day was closer to the task-relevant position axis than on the first day for the long training schedules. However, the specificity of the applied force pattern on the second day was affected by both the washout period and training duration. That is, the learning trajectory on the second day was farther from the position axis for the short training conditions and when training was followed by a washout period on the first day. Collectively, these data imply that motor adaptation retention and the specificity of the savings are both influenced by training duration, but the magnitude of motor adaptation savings is independent of the exposure duration. These differential effects on motor adaptation retention and savings may reflect the stability and reengagement of implicit and explicit learning mechanisms.

Disclosures: **K.P. Nguyen:** None. **L.C. Bray:** None. **L. Alhussein:** None. **E.A. Hosseini:** None. **W.M. Joiner:** None.

Poster

806. Motor Learning: Behavior

Location: Hall A

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Program#/Poster#: 806.28/V20

Topic: D.17. Voluntary Movements

Support: Australia Research Council

Title: Savings requires prior history of error, not repetition of successful movements

Authors: *L.-A. LEOW[1], A. DE RUGY[2], S. RIEK[3], W. MARINOVIC[4], T. J. CARROLL[5]; [1]Sch. of Human Movement and Nutr. Sci., Brisbane, Australia; [2]Univ. de Bordeaux, Bordeaux, France; [4]Sch. of Human Movement and Nutr. Sci., [5]Sch. of Human Movement And Nutr. Sci., [3]The Univ. of Queensland, Brisbane, Australia

Abstract: When we move, perturbations in the environment often elicit discrepancies between predicted and actual movement outcomes. We readily adapt our movements to correct these prediction errors, and this learning can show savings. That is, after initially adapting to a perturbation and then executing movements in an unperturbed environment (washout), re-adaptation to the original perturbation can be faster. Recent data suggest that when we learn, we increase our sensitivity to the errors we experience, and that savings results from improved trial-by-trial corrections of previously experienced errors at subsequent learning (Herzfeld et al., 2014). An alternative theory suggests that savings occurs when an action that successfully reduces errors is reinforced through repetition, and this reinforced action is more rapidly selected at subsequent learning (Huang et al., 2011). Here, in a factorial design, we sought to dissociate how prior experience of error and repetition of successful movements affect savings. The perturbation was a rotation of visual feedback of hand position. All conditions contained the following blocks: A1: 30° CW (clockwise) rotation, Washout: no rotation, B: 30° CCW (counterclockwise) rotation, and A2: 30° CW rotation. Savings was assessed in B. Conditions were as follows: NoErrorNoRepetition, NoErrorPriorRepetition, PriorErrorNoRepetition, PriorErrorPriorRepetition. In all the NoError conditions, the A1 CW rotation was gradually imposed and gradually removed, such that the same CCW errors as B were never previously experienced. In all the PriorError conditions, the A1 rotation was abruptly imposed and abruptly removed, such that the same CCW errors as B were only experienced after the rotation was abruptly removed. In all the PriorRepetition conditions, target location was manipulated to induce repetition of a successful movement, such that the movement solution to hit the target was the same throughout A1 to B. In all the NoRepetition conditions, target location was manipulated such that the movement solution to hit the target never repeated before block B. Error x Repetition ANOVAs on rate constants of exponential fits on block B directional errors showed significant main effects of Error ($p=.03$), no significant main effects of Repetition, and no significant Error x Repetition interaction (all $p>0.05$). Hence, prior experience of errors appears both necessary and sufficient for savings, whereas reinforcing a motor action via repetition appears neither necessary nor sufficient for savings.

Disclosures: L. Leow: None. **A. de Rugy:** None. **S. Riek:** None. **W. Marinovic:** None. **T.J. Carroll:** None.

Poster

806. Motor Learning: Behavior

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Program#/Poster#: 806.29/V21

Topic: D.17. Voluntary Movements

Support: NSF Grant 1358756

Title: A rapid-response-selection model of motor skill: learning to produce low-latency responses to arbitrary visual stimuli

Authors: *R. M. HARDWICK, J. W. KRAKAUER, A. M. HAITH;
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Abstract: Motor skill involves not only selecting appropriate actions and executing them well, but also being able to do so with a low latency. For instance, two goalkeepers can be equally skilled in executing dives to block a shot, but one who is faster to initiate the appropriate dive is more likely to make a save. Despite the importance of response latency, most models of motor learning overlook this critical component of skill. Here we examined human subjects' ability to initiate accurate responses at low latency in an abstract motor skill task, and examined the degree to which this could be improved with practice. Participants first learned an arbitrary association between symbolic cues and movements to spatial targets. Once these associations were established, we determined the speed-accuracy trade-off, between preparation time and response accuracy, using a timed response paradigm (Ghez et al., Exp Brain Res, 1996) in which participants initiated movements at a precise time within each trial. We manipulated the amount of preparation time allowed to initiate a response by varying the time of presentation of the cue relative to the time of movement onset. Participants exhibited a clear speed-accuracy trade-off, with the proportion of correct responses increasing monotonically as a function of preparation time. Critically, training led to an improvement in this speed-accuracy trade-off, reducing the preparation time required to initiate a correct response. We compared behavior to a control condition in which stimulus-response relationships were non-arbitrary (arrows cued the appropriate target). Participants had superior speed-accuracy trade-offs for this non-arbitrary condition, but performance did not change with training. In addition, we compared the speed-accuracy trade-off established in the timed response condition to performance in a choice reaction time condition (i.e. when participants were instructed to move to the correct target as soon as possible after cue presentation). Notably, reaction times in this condition were greater than appeared necessary based on the speed-accuracy trade-off. These results demonstrate that arbitrary visuomotor associations can be viewed as a skill that can be improved with practice over days, and could therefore serve as a useful model of general motor skill acquisition. The ability to initiate accurate responses at low latencies is an important aspect of motor skill, can be enhanced through training, and is not adequately assessed using choice reaction time measures alone.

Disclosures: **R.M. Hardwick:** None. **J.W. Krakauer:** None. **A.M. Haith:** None.

Poster

806. Motor Learning: Behavior

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 806.30/V22

Topic: D.17. Voluntary Movements

Title: Interference between motor memories developed through learning with different arms

Authors: ***N. KUMAR**, P. K. MUTHA;
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Abstract: Learning of a new motor task B shortly after learning another task A is thought to interfere with consolidation of the memory of A. This has been typically demonstrated in studies in which A and B are opposing visuomotor mappings or force perturbations, and are learned with the same arm. The memory for A is generally examined 24 hours after it is initially learned, and similar initial errors and identical rate of learning at these two times are indicators that the intervening learning of B interfered with consolidation of A. Interference presumably arises because the neural substrates mediating learning of A and B are common, which is not surprising because A and B are of the same type and the same arm is used to learn both. However, recent behavioral, neuroimaging and patient studies indicate that regardless of the arm used, the neural substrates mediating motor learning may be the same, and lateralized to the left brain hemisphere. If this is true, then interference between A and B should be observed even if they are learned with opposite arms. Here we tested this idea by having human subjects first adapt to a counterclockwise 30 degree visuomotor rotation (A) and then to a clockwise rotation of the same magnitude (B) with the opposite arm. After 24 hours, subjects were re-tested on A while using the same arm they used during initial learning. We observed complete interference: subjects showed no memory of A and learned at the same rate upon re-exposure as during initial learning. In contrast, we observed protection of the memory of A in control subjects, who learned A and were re-tested on it 24 hours later without learning B; these subjects showed a smaller initial error as well as a faster rate of re-learning. Thus, learning of B prevented consolidation of A even though they were learned with different arms. To the best of our knowledge, such interference between two motor memories, each of which is developed using a different arm, has not been shown before. Our findings lend further support to the idea of a common, possibly lateralized neural substrate for motor learning independent of the arm used to perform the task.

Disclosures: **N. Kumar:** None. **P.K. Mutha:** None.

Poster

807. Brain Machine Interface: Non-Invasive Approaches

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 807.01/V23

Topic: D.18. Brain-Machine Interface

Title: Predicting BCI accuracy with alpha band analysis

Authors: *A. W. AREF[1], J. E. HUGGINS[2];
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Abstract: Brain-Computer Interfaces (BCIs) provide a direct communication pathway between a user's brain and an external device. They can enable communication for people with severe motor impairments. This study used off-line analysis of recorded data where the BCI was used for letter-by-letter spelling. The selections on the BCI display are flashed randomly, and the BCI makes selections based on the event-related potentials in the user's EEG reaction to each flash. To operate the BCI, the user needs to actively attend to selections on the BCI display. Studies have shown that activity in the EEG alpha frequency band (8-13Hz) is negatively correlated with the user's attention to the current task [1]. In this study, recorded EEG from 25 subjects using the BCI was analyzed to determine the correlation between alpha band power and accuracy of BCI selections. For each subject, recorded data included configuration data and BCI use while copying text with correction of errors. Subjects generated at least 23 characters per sentence, 3 sentences per day, for 3 days. The alpha power during the training run was used as the baseline for each subject. Evaluations were made on multiple time-scales (whole-sentence scale and character-by-character scale). The alpha power during each whole sentence was calculated and compared to the spelling accuracy of each sentence. Also, the alpha power before, during, and after each character selection was calculated and compared to the accuracy of each character (1 for correct and 0 for incorrect). The alpha power calculated before and during each character was deemed statistically significant for correct versus incorrect characters with p-values of 0.0018 and 0.00017, respectively. The alpha power before and during the selection of the character showed the most significance, and thus can be used to possibly predict the accuracy of the selection. Classification methods using the alpha power before and during each character as features to predict the accuracy of individual characters, can be used to predict the accuracy of future selections and to block selections that are likely to be inaccurate. 1. Polich, J. "Updating P300: An Integrative Theory of P3a and P3b" Clinical Neurophysiology 118.10 (2007): 2128-148.

Disclosures: A.W. Aref: None. **J.E. Huggins:** None.

Poster

807. Brain Machine Interface: Non-Invasive Approaches

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 807.02/V24

Topic: D.18. Brain-Machine Interface

Title: Silent speech recognition system using single-trial EEGs: A silent season BCI

Authors: *T. ITOH[1], H. YAMAGUCHI[2], A. YAMAGUCHI[3], T. YAMAZAKI[4], S.-I. FUKUZUMI[2], T. YAMANOI[5];
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Abstract: Objective: The purpose of this study is to generalize our silent speech recognition system (SSRS) using single-trial EEGs previously proposed in terms of Japanese vowel recognition. Methods: During actual speeches (the learning phase) and silent ones (the decoding phase) of “haru”, “natsu”,”aki” or ”huju” in English pronunciation of Japanese, representing for seasons, 13-ch single-trial EEGs were recorded. In the learning phase, a relationship between spectrograms of speech signal and independent components (ICs), which are obtained by applying independent component analysis (ICA) to the EEGs, whose equivalent current dipole (ECD) source solutions are localized to the Broca’s area, is described by Kalman filters (KFs).In the other hand, the spectrograms are transformed into sequence of vowels and consonants by hidden Markov model (HMM). In the decoding phase, the EEGs during the silent speeches are inputted to the learned KFs and “silent spectrograms” are estimated by the KFs, then the HMMs, which the estimated spectrograms are inputted to output log- likelihoods with respect to vowel and consonant transition(s). Finally, by comparisons among the log- likelihood values from each HMM, it is determined which season was silently spoken. Results: As a preliminary result, the accuracy was 86% (“haru”), 29% (“natsu”), 43% (“aki”), and 100%(“huju”) for one subject . Conclusions: This study implies the possibility of recognizing and discriminating four kinds of silent speeches in Japanese. In future, we will obtain better accuracy.

Disclosures: T. Itoh: None. **H. Yamaguchi:** None. **A. Yamaguchi:** None. **T. Yamazaki:** None. **S. Fukuzumi:** None. **T. Yamanoi:** None.

Poster

807. Brain Machine Interface: Non-Invasive Approaches

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Topic: D.18. Brain-Machine Interface

Support: NSF Grant 0966963

The Hartwell Foundation

Title: Control of a cursor in two dimensions with one single sEMG signal: Learning a novel motor skill

Authors: *I.-M. SKAVHAUG[1], K. LYONS[1], A. NEMCHUK[2], S. MUROFF[3], S. JOSHI[1]; [1]Mechanical and Aerospace Engin., [2]Psychology, [3]Human Develop., Univ. of California, Davis, Davis, CA

Abstract: We have designed a novel electromyography (EMG)-driven human-computer interface in which a user controls a cursor on a computer screen through low-level muscular contractions. The most novel aspect of our interface is that we create two control channels from one single EMG signal. Subjects achieve two-dimensional control of the cursor by manipulating their EMG power signal in order to simultaneously place a specific amount of power in two separate frequency bands. It is unlikely that this motor skill is needed in any natural body movement. We previously reported a pilot study showing that users can perform this skill using the auricularis superior muscle above the ear. The current study aims to formally study learning in this task from the initial encounter with the device to the end of several practice sessions. A secondary aim of our current study is to investigate this motor skill with a muscle innervated at the spinal cord, rather than the brain stem. 12 naïve able-bodied subjects completed eight one-hour long testing sessions in which they practiced moving a cursor to targets by contracting the extensor pollicis longus muscle located on the wrist. Performance measures included success rates, time-to-target (in seconds) and the percentage of time which the cursor spent in the desired section of the screen during any trial. We show that average subject success rates rapidly improved throughout the first three testing sessions and continued to improve throughout the remaining five sessions (however at a slower rate). At the end of 8 training sessions, the group achieved an 86% success rate for target hitting. Correspondingly, the time-to-target steadily decreased throughout all eight sessions. Most importantly, the percentage of time the cursor spent in the vicinity of the goal target increased significantly across the experiment for both successful and unsuccessful target hits, suggesting that with experience the subjects gained better control of the cursor's movement. Overall, we conclude that subjects significantly increase their ability to use our myoelectric interface throughout a relatively short training program of eight hours.

Disclosures: **I. Skavhaug:** None. **K. Lyons:** None. **A. Nemchuk:** None. **S. Muroff:** None. **S. Joshi:** None.

Poster

807. Brain Machine Interface: Non-Invasive Approaches

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Topic: D.18. Brain-Machine Interface

Support: Hartwell Foundation

NSF

Title: Control of a cursor in two dimensions with one single sEMG signal: Effects of muscle fatigue

Authors: I.-M. SKAVHAUG, A. G. BARSZAP, *S. S. JOSHI;
Mechanical and Aerospace Engin., Univ. of California, Davis, Davis, CA

Abstract: Electromyography (EMG) has long been employed in prosthetics control, and more recently, EMG has also been utilized in Human-Computer Interfaces (HCI) for the disabled. A common concern relating to all EMG driven devices is the potential loss of performance due to fatigue. Here, we investigate the effects of fatigue on a single muscle-site EMG HCI, in which subjects navigate a cursor to targets by making low level contractions of a muscle. Subjects achieved two-dimensional control of a computer cursor by varying the power in two separate frequency bands (80-100Hz and 130-150Hz) of a single EMG signal. Two groups of four subjects (one group using a head muscle and the other group using a wrist muscle) completed 300 cursor-to-target trials (approximately 3 hours of use without breaks) during which we monitored performance. The wrist muscle group also returned for a second session, in which they completed an additional static fatigue-inducing exercise between each block of thirty trials. We did not observe any clear evidence of fatigue during the first session (for either group). During the second session (with fatiguing exercises) subjects' performance declined steadily towards the end of the experiment and we also observed an apparent difficulty in moving the cursor in the y-direction. This specific change in cursor trajectories was consistent with a shift of the median frequency towards the left in the power spectrum. This type of spectral compression has been reported previously in the literature for static isometric contraction (as opposed to our case which is a dynamic low level contraction). We conclude that fatigue is not a major concern

during normal use of our EMG-driven interface, but may be problematic after unlikely extreme and sustained use.

Disclosures: I. Skavhaug: None. **A.G. Barszap:** None. **S.S. Joshi:** None.

Poster

807. Brain Machine Interface: Non-Invasive Approaches

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 807.05/V27

Topic: D.18. Brain-Machine Interface

Support: INDIREA

Title: Neurophysiological correlates of mind-wandering, towards a predictive BCI

Authors: *A. MARTEL[1], P. DOCKREE[2], I. ROBERSTON[3];
[2]TCD Sch. of Psychology, [3]TCD Inst. of Neurosci., [1]Trinity Col. Dublin, Dublin, Ireland

Abstract: Neuroscientific evidence has determined that our ability to remain attentive to a task, over a prolonged period of time, is subject to strong fluctuations. Recent electroencephalography (EEG) studies have identified neurophysiological signals reflecting inadequate task engagement preceding attentional lapses. Smallwood et al. (2008) investigated mind-wandering episodes on subjects performing the sustained attention to response task (SART) (Robertson et al. 1997), with thought probes and unveiled a significant reduction of the P300 amplitude during the reported mind-wandering episodes relative to the on-task periods. O'Connell et al. (2009) observed a modulation of the α-activity 20 s and of the P3 four to five s before a lapse of attention in a temporal expectancy task. Martel et al. (2014) found a decrease in P3 amplitude and increase in α-activity foreshadowing a miss by up to 10 s in a covert sustained attention task. Lapses of attention during mind-wandering episodes are the result of a withdrawal of attention from the task at hand towards internal, self-generated thought processes, or personal information such as memories (Smallwood et al. 2006). The present study recorded EEG, pupillometry, respiration and galvanic skin response (GSR) of twenty-six participants during a breath-counting task and a fixed version of SART with thought probes. During the breath counting-task subjects fixated on a cross while counting each inhalation from 1 to 9, pressing the left mouse button for 1 to 8 and the right button when reaching 9 before starting counting again. The SART presented participants with numbers from 1 to 9 sequentially and required them to respond for all numbers except 6, for which they were required to withhold response. Thought probes would randomly interrupt the task after 30 to 120 s on-task and prompt subjects to report whether their attention

was on-task, on thoughts related to the task, distracted by exogenous or endogenous stimuli, on planning or reminiscing, or on daydreams. Subjects were also instructed to interrupt the task if they caught themselves being inattentive. Preliminary results corroborate previous finding of P3 amplitude attenuation and differences in oscillatory activity between on-task and mind-wandering episodes. Additional analysis with Brain-computer interface (BCI) methods (SPoC - Dähne et al. 2014 & CSP - Blankertz et al. 2008) will determine whether mind-wandering episodes can be predicted in real-time and inform the participant for prospective use in a Neurofeedback training (NFT).

Disclosures: **A. Martel:** None. **P. Dockree:** None. **I. Roberston:** None.

Poster

807. Brain Machine Interface: Non-Invasive Approaches

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Topic: D.18. Brain-Machine Interface

Support: FINEP 01.12.0514.00

AASDAP

AACD

Itau Bank

Title: Cortical incorporation of virtual legs in Spinal Cord Injured patients

Authors: R. MOIOLI[1], S. SHOKUR[2], S. GALLO[3], F. BRASIL[1], *E. MORYA[1], M. NICOLELIS[4,1,5];
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Abstract: Spinal cord injury (SCI) induces spontaneous plastic reorganization of the body representation at cortical level. Here, we studied whether incorporation of a virtual body part related to an actual paralyzed leg could become part of a novel neurorehabilitation paradigm towards restoring mobility in paraplegic patients. Eight SCI paraplegic subjects (seven complete ASIA A and one incomplete lesion ASIA B) signed a consent form (IRB 364.027), and

underwent virtual reality walking sessions while their EEG was recorded. To perform this task they wore an immersive virtual reality head mounted display. Subjects observed legs of an avatar overlapped with their own as if they were continuation of their physical body. Tactile feedback from the virtual limbs was delivered using a haptic display attached to the subjects' forearm skin surface. Such feedback was delivered in accordance with the avatar walking. EEG recording was synchronized with the delivery of tactile feedback while the avatar walked. Visuo-tactile related cortical reorganization was detected in sensory-motor and multi-sensory brain areas. These findings are in accordance with previous observations during incorporation of an external body part. Therefore, we propose that sensory substitution (using the forearm to map feedback from legs) can be used to embed a new cortical representation of lower limbs, via assimilation of avatar limbs, and help in the process of neurorehabilitation of these patients.

Disclosures: R. Moioli: None. **S. Shokur:** None. **S. Gallo:** None. **F. Brasil:** None. **E. Morya:** None. **M. Nicolelis:** None.

Poster

807. Brain Machine Interface: Non-Invasive Approaches

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Topic: D.18. Brain-Machine Interface

Support: FINEP 01.12.0514.00

AASDAP

AACD

Itau Bank

Title: Inducing paraplegic patients to perceive distinct ground textures using tactile feedback generated by virtual feet

Authors: *S. SHOKUR[1], S. GALLO[2], R. MOIOLI[3], M. BOURI[2], E. MORYA[3], H. BLEULER[2], M. LAPORTA NICOLELIS[3,4,5];
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Abstract: Spinal Cord Injury (SCI) induces bidirectional loss of communication between the brain and the body and between the brain and the external world. SCI patients neither control nor sense the body below the level of their injuries. We have proposed a solution for functional restoring sensory-motor control during locomotion for paraplegic patients (M.A.L. Nicolelis et al. The Walk Again Project: Using a Brain-Machine Interface for establishing a bi-directional Interaction between paraplegic subjects and a lower limb exoskeleton. Program No. 636.18/MM25. Neuroscience 2014 Abstracts. Wahsington, DC: Society for Neuroscience, 2014. Online). Eight SCI patients (seven with complete injury (ASIA A) and one with incomplete injury (ASIA B)) were trained to walk both in a simulated virtual environment and with a custom exoskeleton by imagining leg movements. Tactile feedback from the exoskeleton's feet surface was remapped on the patients forearm using arrays of mechanovibrators. Patients could rely on this tactile feedback to sense the position of the leg and the exo's contact with the floor. Here, we show how, by changing parameters of the tactile feedback, patients experienced the sensation of walking on different ground surfaces, such as: beach sand, a paved street or a grass field. For each patient, ten thousand combinations of tactile feedback were obtained by varying the amplitude, the duration and the time between vibrations. Patients were asked to select among all possible combinations the ones that corresponded to the sensation of walking on the aforementioned ground types while looking to an avatar walking on the corresponding ground or on a neutral black ground. The majority of the patients could find a combination of vibrotactile parameters that gave them a realistic sensation of walking on the selected ground. Patients' ground choices usually relate to the tactile sensation experienced at the very end of the stance phase. Overall, ground parameters were similar among groups of patients, suggesting that, despite being paralyzed for many years, patients shared similar representations of ground surface. We propose that future neuroprosthetics for locomotion will have to incorporate tactile feedback to achieve optimal performance and for provide patients with more realistic walking sensations. Acknowledgments: The authors thank Alberto Santos Dumont Association for Research Support (AASDAP), Finep and the 156 people involved in this project.

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Poster

807. Brain Machine Interface: Non-Invasive Approaches

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AASDAP

AACD

Itau Bank

Title: Twelve month of physical rehabilitation protocol integrating brain controlled locomotor training and tactile feedback for patients with chronic spinal cord injury

Authors: *A. C. DONATI[1,2], S. SHOKUR[1], E. MORYA[3], C. GITTI[1,2], P. AUGUSTO[1,2], G. DIAS[1], D. CAMPOS[1,2], D. YOSHIHARA[1,2], M. LAPORTA NICOLELIS[4,5,3];
[1]Associacao Alberto Santos Dummont Para Apoio A Pes, AASDAP, Sao Paulo, Brazil; [2]Associacao de Assistencia a Crianca Deficiente (AACD), Sao Paulo, Brazil; [3]Edmond and Lily Safra Intl. Inst. of Neurosci., Inst. Santos Dumont, Macaiba, Brazil; [4]Neurobiology, Biomed. Engineering, Psychology and Neurosci., Duke Univ., Durham, NC; [5]Duke Ctr. for Neuroengineering, Durham, NC

Abstract: Spinal cord injury (SCI) is considered a public health challenge, with devastating consequences on the subject himself. Here, we investigated the clinical effects of a novel neuroreabilitation program for paraplegic patients based on the concept of brain-machine interfaces (BMI). Eight subjects with chronic spinal cord injury (paraplegia) participated in the study, seven of them with complete injury (ASIA A) and one with incomplete injury (ASIA B). They pursued an intensive training for twelve months with activities included traditional physical therapy exercises, body-weight support (BWS) system for gait training (BWS ambulation on a treadmill and BWS ambulation on a fixed overground track), but also a brain-controlled robotic gait (or Brain Machine Interface BMI) training triggered by EEG and with the sensory support of tactile feedback. Patients' physical and emotional levels were assessed during twelve months. After 12 months of training, patients showed better control of intestinal function and improvements of the cardiovascular and neurological systems. Most patients also regained some muscular activities below the level of SCI. They also exhibited an increase of the somatosensory sensitivity below the level of SCI and an improvement in the zone of partial pain tactile sensation. As a result of this neurological improvement, three of the subjects moved from a complete (ASIA A) to incomplete (ASIA C) injury classification. These results suggest that chronic BMI utilization may lead to a degree of neurological improvement. Further studies are under way to clarify the potential mechanism underlying the neurological recovery observed here.

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Poster

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AASDAP

AACD

Itau Bank

Title: Walk using single leg control at BMI-driven exoskeleton

Authors: *F. L. BRASIL[1], S. SHOKUR[2,3], M. ALBANO DE ARATANHA[1], R. CIPRIANO MOIOLI[1], A. CORTELLI DONATI[2], E. MORYA[1], M. LAPORTA NICOLELIS[4,5,1]; [1]Edmond and Lily Safra Intl. Inst. of Neurosci., Inst. Santos Dumont, Macaiba, Brazil; [2]Alberto Santos Dumont Assn. for Res. Support, São Paulo, Brazil; [3]Edmond and Lily Safra Intl. Inst. of Neurosci, Macaíba, Brazil; [4]Professor of Neurobiology, Biomed. Engineering, Psychology and Neurosci., Durham, NC; [5]Co-Director, Duke Ctr. for Neuroengineering, Durham, NC

Abstract: By establishing direct communication between a subject's brain and external actuators, brain-machine interface (BMIs) have been heralded as potential new therapeutic alternatives for spinal cord injury (SCI). Here we tested a BMI in which EEG signals were decoded in real time to detect voluntary movement of legs and control a custom brain-controlled exoskeleton (EXO). Our EXO uses an hydraulic pump and transmission to ensure patient's balance and control of autonomous bipedal locomotion, without the need for auxiliary tools, such as crutches. Six SCI patients (five of them with complete injury (ASIA A) and one with incomplete injury (ASIA B)) participated in this study. They were instructed to imagine moving their left and right legs to control the forward stepping of the ipsilateral EXO legs. By alternating the left and right motor imagery, all patients became proficient in controlling the EXO during walking. This was achieved by using a shared-control mode of EXO operation in which, patients were in charge of high level walking commands, while the EXO calculated the low level kinematics and balance/stability control. Our results demonstrate the feasibility of using a brain-controlled EXO as an assistive walking device for SCI patients. Acknowledgments: The authors thank Alberto Santos Dumont Association for Research Support (AASDAP), Finep and the 156 people involved in this project.

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Poster

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AASDAP

AACD

Itau Bank

Title: Closed loop brain controlled avatar training for locomotion with spinal cord injured patients

Authors: ***M. A. ARATANHA**[1], S. SHOKUR[2], F. LIMA BRASIL[1], A. CORTELLI DONATI[2], S. GALLO[3], E. MORYA[1], M. LAPORTA NICOLELIS[4,5,6];
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Abstract: Five spinal cord injury (SCI) patients (four with complete lesions and one with an incomplete lesion) were trained to use their cortical activity, recorded using EEG, to control the movements of virtual avatar legs seen from their first person perspective through a head mounted display. Every time the avatar feet touched a virtual floor, patients received tactile feedback describing that contact. Tactile feedback was delivered through three mechano-vibrating elements placed on each of the patient's legs; two on the knee and one on the hip. While our patients could not directly feel feedback on their leg skin, all of them reported feeling the vibrations when they were applied over the bone. EEG was recorded and decoded in real time while patients were instructed to imagine the avatar as part of their body and move the virtual left and right legs in an alternated sequence. Detection of leg motor imagery in the EEG was

used to trigger the movement of the corresponding leg on the avatar. Patients successfully learned to control both the avatar walking and stopping in this virtual environment. Following a session where a synchronous visuo-tactile feedback was delivered, two patients improved the ability to discriminate between different vibrator positions. Acknowledgments: The authors thank Alberto Santos Dumont Association for Research Support (AASDAP), Finep and the 156 people involved in this project.

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Poster

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Title: A longitudinal evaluation of SSVEP-BMI in patients with ALS

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Abstract: Brain-machine interface (BMI) or brain-computer interface (BCI) is an interface technology that utilizes neurophysiological signals from the brain to control external machines or computers. We have developed a P300-based BMI system to support daily activities of persons with disabilities, and found that green/blue chromatic and luminance flicker matrices improved the BMI performance (Takano et al., 2009). We showed that the P300-based BMI can be satisfactorily used by patients with spinal cord injury and amyotrophic lateral sclerosis (ALS) (Ikegami et al., 2011; 2014). We also showed that the use of high-frequency visual stimuli provided high classification accuracy in a steady-state visual evoked potential (SSVEP)-based BMI (Sakurada et al., 2015). In this study, we used a high-frequency SSVEP-based BMI system,

and tested the system for six months (longitudinal evaluation). We performed the experiments once every 1 or 2 weeks. To elicit SSVEPs, we prepared a light-emitting diode (LED) flicker using a visual stimulus apparatus with green/blue LEDs covered by a diffusion board. This system consisted of a PC, an EEG amplifier and 1-3 LEDs (34 to 54 Hz). Single channel (Oz) EEG data was recorded with in-house caps and solid-gel electrodes (Toyama et al., 2012). The EEG was digitized at a rate of 1024 Hz and stored. The SSVEP-based BMI performance was evaluated by calculating the power of the EEG data. Three ALS patients (2 males, 37-64 years old, ALSFRS-R = 0) participated in this study. One of the patients could not use the augmentative and alternative communication (AAC) devices and other patients were able to control conventional AAC devices. The mean accuracy of all experiments was 79.1% (n=3). At the first one-month measurement, the accuracy of each patient was 75.0%, 67.0% and 75.0%, respectively, and at the last one-month measurement, the accuracy of each patient was improved to 85.4%, 91.7% and 89.6%, respectively. Note that one of the patients could not use AAC devices but was able to use our system with practical accuracy (>70%). In this longitudinal evaluation, the ALS patients were able to use the SSVEP-BMI system satisfactorily. This suggests that the SSVEP-BMI system is beneficial in patients with ALS.

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Poster

807. Brain Machine Interface: Non-Invasive Approaches

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Support: NIH/NIBIB & NINDS (EB00856)

NIH/NIDCD (R21 DC010470-01)

Title: Performance comparison of color and grey-white paradigms in undergraduates and older adults using the brain-computer interface

Authors: ***S. SPRAGUE**, D. B. RYAN, M. R. KELLICUT-JONES, T. L. STREET, E. W. SELLERS;
Psychology, East Tennessee State Univ., Johnson City, TN

Abstract: Amyotrophic lateral sclerosis and other neurodegenerative disorders can cause individuals to lose control of their muscles until they are unable to move or communicate. Brain-computer interfaces (BCIs) can provide an alternative method of communication that does not require muscle movement; however, BCI provides a slow form of communication. Therefore, many researchers focus on increasing speed and accuracy. One method for increasing the speed and accuracy of the BCI is by creating and manipulating the paradigms that control how the stimuli are presented. The aim of the present study is to compare the speed and accuracy of two different presentation paradigms in two non-disabled populations: traditional college aged students and those over the age of 45. The first experimental paradigm presents grey characters that change to white. The second paradigm presents color characters that temporarily disappear. Hypothesis 1: Younger participants would score better on performance measures than older adults. Hypothesis 2: Participants would score better on performance measures in the color paradigm than in the grey-white paradigm. We compared three performance measures: accuracy, speed, and bit rate. None of the three measures showed statistically significant differences by group, nor was the accuracy measure statistically significant by condition. On the other hand, both the young and older groups were able to make selections significantly faster in the color condition than in the grey-white condition. Moreover, both the young and older groups had higher bit rates in the color condition. Participants also completed a preference survey after each condition. The survey included three questions: I was able to focus on the target item; non-target items were distracting; and it was difficult to see all the target flashes. Participants used a Likert scale to indicate whether they strongly disagreed (1) with each statement or strongly agreed (7). Despite being able to make selections significantly faster in the color condition as well as higher bit rates, the survey items did not reveal a preference for one condition over the other. More data is needed in order to determine which paradigm is superior in both accuracy and preference.

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Poster

807. Brain Machine Interface: Non-Invasive Approaches

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Topic: D.18. Brain-Machine Interface

Support: NIH/NIDCD (4R33 DC010470-03)

Title: Utilizing visual attention and inclination to facilitate brain-computer interface design in an amyotrophic lateral sclerosis and college age sample

Authors: *D. RYAN[1], M. L. MORTON[2], E. W. SELLERS[2];
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Abstract: Thus far research has not addressed the issue of finding the optimal paradigm to fit an individual's visual attention abilities. Traditionally, in-home BCI applications rarely deviate from a "standard" paradigm. The norm to improve poor performance is a trial and error method, which is only employed in patient populations. This study proposes to identify the best paradigm for an individual by systematically manipulating flash type, stimulus size, and flash duration. We hypothesize that this method will reveal an optimal paradigm that outperforms a standard (control) paradigm. Additionally, the majority of BCI research is conducted with college age (18-22 years) participants. This is an issue because there are well documented changes in the ERP responses as a result of age (Braver et al., 2001; West, Schwarb, & Johnson 2010). Furthermore, there could be changes to the P300 and other ERP components as a result of ALS progression. To examine these changes and their potential influence on BCI performance, we have collected data from participants with ALS and from college age participants. The results from t-tests within participant groups showed that participants with ALS had a significant increase in BCI performance in the optimal condition over the standard condition. The college age participants did not show any significant performance differences between conditions. In a 2x2 repeated measures analysis (participant groups x conditions) we found a main effect of Accuracy, main effect of Logit transform of accuracy, and a main effect of Survey. These results show that the method used to examine the BCI performance and personal preference resulted in an optimal paradigm that was better by performance and preference measures compared to the standard paradigm. When examining the waveforms from the control condition (to keep stimuli consistent) we see that college age participants have stronger ERP amplitude responses than those with ALS. This stronger response allows the classifier to make higher accuracy discriminations between target and nontarget responses with less data (i.e., less flashes). Thus, higher amplitude ERP responses and BCI performance from younger participants do not accurately reflect the ERP responses and performance found in an ALS sample. Therefore, BCI research should shift its focus to an ALS population or at least age-matched control participants rather than college age participants.

Disclosures: D. Ryan: None. **M.L. Morton:** None. **E.W. Sellers:** None.

Poster

807. Brain Machine Interface: Non-Invasive Approaches

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Topic: D.18. Brain-Machine Interface

Support: NIH/NIDCD (4R33 DC010470-03)

Title: P300 brain-computer interface:comparing faces and size-matched non-face stimuli

Authors: ***M. R. KELLICUT**[1], C. M. COFFMAN[2], D. B. RYAN[2], E. W. SELLERS[2];
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Abstract: Non-invasive Brain Computer Interface (BCI) technology can restore communication for those who are no longer able to communicate to due loss of muscle control. Nonetheless, in comparison to other methods of non-muscular communication, such as an eye tracker, BCIs provide relatively slow communication. Therefore, it is important to implement techniques that can improve both accuracy and speed of BCI performance. One method of improving accuracy in BCI performance has been the presentation of familiar faces rather than the canonical presentation whereby the characters in an alphanumeric display change from grey to white. Previous studies have shown that in addition to the P300 event-related potential component faces elicits the N170 and N400 components. The addition of these components can increase the speed and accuracy with which items can be selected from the display. Previous studies have used face stimuli that are typically much larger than the items contained in the display. The purpose of the present study was to investigate the influence of image size and image content. Based on the results of previous studies, we predicted that faces would provide higher accuracy than non-face stimuli. To test this hypothesis we designed four conditions: large face stimuli, small face stimuli, large non-face stimuli, and small non-face stimuli. The familiar image of Albert Einstein sticking his tongue out was used as the face image. The non-face image was constructed using a crystalize filter (Photoshop CS5.5) and rotating it 180 degrees, thereby preserving the image content while making the stimulus unrecognizable as a face. The “checkerboard” paradigm was used to present stimuli and a Latin square design was used to determine the order of presentation: The preliminary data indicate there are no statistically significant differences between the four conditions. Nevertheless, mean accuracy in the small crystalized stimulus condition was higher than the small face, large face, and large crystalized conditions. Additional data will be collected to further test the hypothesis that face stimuli provide higher rates of speed and accuracy.

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Poster

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Support: German Research Foundation, DFG Grant BR 1691/8-1

Title: How individual is low-voltage brain stimulation, rebound or entrainment? The influence of 10 Hz alternating current stimulation on the individual alpha rhythm

Authors: *S. SCHMIDT[1], L. HABERBOSCH[2], A. JOOß[2], A. KÖHN[2], M. SCHOLZ[3], K. OBERMAYER[3], S. A. BRANDT[2];
[1]Vision & Motor Res. Group, Berlin, Germany; [2]Neurol., Charité Universitätsmedizin - Berlin, Berlin, Germany; [3]Neural Information Processing Group, Univ. of Technol., Berlin, Germany

Abstract: Introduction: Alternating current stimulation (ACS) is an established means to modulate neural oscillations. Retinofugal alternating current stimulation (rtACS) is a novel and promising application of ACS. It has shown effects on neural oscillations outlasting the stimulation duration and allows investigation of stimulation effects in the well-circumscribed visual system. Neuromodulatory effects of ACS have been associated with significant behavioral and clinical impact, but the mechanism of action remains unclear and the notion of individualized stimulation unresolved. Possibilities include neuronal entrainment as well as rebound phenomena. A possible frequency peak shift from individual alpha towards the stimulation frequency would contribute to the discussion and support the notion of entrainment. The lack of a shift supports the notion of post-inhibitory rebound. Therefore, we investigated the alpha band peak before and after 10 Hz electric (rtACS) and photic stimulation ("photic driving"). Methods: To address this question, we stimulated 8 healthy subjects with "photic driving" or rtACS at a frequency of 10 Hz while recording EEG. Prior to stimulation, we assessed electrode impedances and phosphene thresholds and recorded a resting state EEG. We then applied rtACS in 6 blocks of 30s stimulation. We then assessed the spectral alpha power as well as the alpha peak frequency (individual alpha) over the occipital electrodes during baseline and 30s after stimulation and compared the two in a repeated-measure ANOVA. Results: A significant enhancement of α power was found during as well as after photic and electric stimulation. The alpha peak frequency changed by a mean 0.02 Hz (+/- 0.04) following rtACS and 0.03 Hz (+/- 0.05)) following photic driving. There was no evidence for a significant frequency peak shift or an association between stimulation frequency and alpha power change. Conclusions: The data at hand provides evidence against entrainment effects better in line with post-inhibitory rebound. Post-inhibitory rebound could provide stabilization and enhancement of an intrinsic frequency following a period of inhibition. Still, previous data suggest that post-inhibitory rebound is possibly not well equipped to explain neuromodulatory effects or photic

driving. As neural oscillators share features of both harmonic and relaxation oscillators, one mechanism of action may be a combination of both entrainment and rebound, where short periods of exogenous entrainment are followed by a rebound-like recruitment of similarly patterned endogenous oscillators.

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Poster

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DFG Grant BR 1691/8-1

Title: The stationary brain? -adaptive, feedback controlled electric stimulation, a case study-

Authors: *M. SCHOLZ[1], S. SCHMIDT[2], L. HABERBOSCH[2], A. JOOß[2], S. A. BRANDT[2], K. OBERMAYER[1];
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Abstract: Our brain is a highly dynamic system. Transcranial and -orbital electric stimulation is a promising technique to help the beneficial reorganization of disease affected parts of the brain, from stroke to insomnia, visual to motoric deficits, spanning a wide field of possible clinical or even homecare applications. The used current could be DC (tDCS), AC (tACS) or random (tRNS) and is generally applied over 10-20min. Although the literature is somewhat controversial, common to most publications is a high percentage of “non-responders” and a static stimulation scheme, which is not adapted throughout the experiment. However, due to the intrinsic plasticity of the brain and its highly dynamic behavior, described but not precisely defined as “brain states” it seems likely, that the stimulation itself should change during the course of an experiment/treatment to reflect altered brain states and progress of learning. We address this here by using a new, selfadapting stimulation paradigm characterized by repeating short (~5s) cycles of stimulation and measurement. To be able to adapt the stimulus quickly on the fly, the following prerequisites must be met: i) a fast (under a second) evaluable state

variable, such as amplitude power in a specific frequency or cortico-muscular coherence, ii) a proof-of-principle that repeated short term stimulations have a comparable effect as 10min static stimulations and iii) a noise robust optimization scheme, such as evolutionary algorithms. As a testbed for this scheme, we used a well understood paradigm. Stimulating the optic nerve with 2 transorbital electrodes with 5-15Hz sine waves we analyze resulting alpha burst power in eyes open and closed conditions differentiating between rebound and entrainment, comparing it to classical long term stimulation. Since the Berger phenomenon is very stable and well understood, this scenario was chosen to show the reliability and robustness of such a closed-loop paradigm, because little is known about expected behavior and ground truth for other subsystems of the healthy brain. Where science still lacks a mathematical good description of the state trajectories of a healthy brain, things become even more speculative in the much more challenging field of stroke rehabilitation, where the brain is not normal or healthy. Even if we could reliably estimate which exact stimulus causes a specific behavioral change, it seems unjustified to assume that this will hold for a trauma induced change. With our proposed closed-loop approach not only subject specific differences but also such gross structural (brain) system changes could be successfully addressed as is the case in stroke restitution.

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Poster

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Support: STW grant 12803

Title: Quantification of target population for communication brain computer interfaces in the Netherlands

Authors: ***E. G. M. PELS**, E. J. AARNOUTSE, M. J. VANSTEENSEL, N. F. RAMSEY; Brain Ctr. Rudolf Magnus, Univ. Med. Ctr. Utrecht, Utrecht, Netherlands

Abstract: The target population for brain computer interfaces (BCI) for communication is predominantly described as locked-in syndrome (LIS) patients (Birbaumer et al 2008). From a BCI point of view, this population encompasses all patients with severe communication impairment due to severe paralysis regardless of the etiology. The medical definition of LIS is

exclusively defined by lesions in the ventral pons, not by the level of functioning or the needs of the patient (Meienberg et al 1979, Balami et al 2013). The constrained definition of LIS poses an obstacle for developers of communication BCIs and for other stakeholders like caregivers, families and companies, who stand to benefit from a more inclusive definition of the patient population for care, information and assistive technology development. Therefore we argue that in order to quantify the target population for BCIs all patients that function on the level of LIS (fLIS) should be considered, disregarding etiology. Efforts to calculate LIS prevalence before (Kohnen et al 2013; Snoeys et al 2013) only partially succeeded To estimate prevalence of fLIS, we sent out a letter to all, 8783, general practitioners (GPs) in the Netherlands covering the whole population (16 829 289; Statistics Netherlands, 2014) asking whether they were treating a patient with severe paralysis. The response rate was 15.5%, a subset of which responded affirmative. Those GPs were subsequently approached by telephone and asked to complete a questionnaire consisting of 22 items on the level of functioning, the cause of paralysis and the type of care and assistive technology used. After screening 11 patients were labeled with fLIS. An extrapolation of these results indicate a prevalence of 0.42 cases per 100 000 inhabitants. Moreover, the results of the questionnaires indicate, regardless of the cause of disability, care is similar, e.g. most patients are dependent on tube-feeding and most patients rely on homecare and artificial ventilation. Communication on the other hand showed a very diverse landscape. A wide range of alternative communication devices are used: eye trackers, mouth-stick, (spoken) letter boards and EEG/EMG device. The current research shows that there is a significant population in the Netherlands that functions on the level of LIS. Furthermore, care needed by patients is similar. Labeling the population by function and needs would help patients, caregivers and augmented alternative communication developers to gain coherence and visibility.

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Poster

807. Brain Machine Interface: Non-Invasive Approaches

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 807.18/V40

Topic: D.18. Brain-Machine Interface

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EU COST action TD1006

Title: EEG decoding of Arm reaching and hand movements

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Abstract: The ability of Brain-Computer Interface (BCI) systems to decode functional movement parameters based on electroencephalographic (EEG) data to control a robotic exoskeleton in post-stroke rehabilitation is of clinical importance. Most of the previous studies have addressed the classification of two or three classes mainly using imagery or motion or different limbs or within same limb for characterization of two classes. To date, there are not many studies exploring the decoding of functional hand movements from the same limb. We designed and developed an experiment to investigate functional upper limb movements attaching a newly developed exoskeleton to healthy volunteers upper limb. This study explores EEG decoding during a three-dimensional (3D) center-out arm reaching (four directions and Rest) and five hand movements (grasp, pinching, pointing, pronation, supination), all executed with the same limb. Nine healthy volunteers underwent EEG recordings in 4 sessions. Data was preprocessed and artifacts were eliminated. We used a 5-class BCI design to classify EEG signals related to four directions and Rest, and 6-class design for five different hand grasping movements and Rest based on a multi class extension of Spectrally Weighted Common Spatial Patterns (Spec-CSP) and a linear discriminant analysis (LDA) classifier. For illustrative purposes, we compared the r2 values as feature maps at individual frequencies and channel

locations between two tasks and performed also a topographical distribution analysis of Spec-CSP patterns of each condition-pair. Decoding accuracies were 39.5% (chancel level of 20%) and 24.6% (chance level of 16.6%) for the 5-class directional movements and the 6-class hand movements, respectively. The confusion matrices showed that space resolution (neighbored movements confused) and similar hand configurations were the main limitation for our decoding approach during direction and grasping movement respectively. These results were significantly above chance level and indicate that multiple functional movements classification from the same limb may be possible using EEG data, although further experiments are needed to leverage these results to a more functional level. We propose the combination of "less confused" functional movement and a probabilistic output method to improve functional upper limb movements classification using EEG data.

Disclosures: F. Shiman: None. **N. Irastorza-Landa:** None. **A. Sarasola:** None. **M. Spüler:** None. **N. Birbaumer:** None. **A. Ramos-Murguialday:** None.

Poster

807. Brain Machine Interface: Non-Invasive Approaches

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Topic: D.18. Brain-Machine Interface

Support: NIH-NIGMS 5R25 GM 096161

Cerbomed GmbH, Erlangen, Germany

Title: Effective connectivity analysis of brain regions responsive to non-invasive vagus nerve stimulation in humans

Authors: *E. FRANGOS, B. R. KOMISARUK;
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Abstract: We recently published fMRI evidence (Frangos et al., Brain Stimul., 2014, doi:10.1016/j.brs.2014.11.018) that a non-invasive approach to vagus nerve stimulation activates the classical central projections of the vagus nerve including regions that have a neuromodulatory role in pain, depression, and epilepsy. The present study was undertaken to analyze the connectivity pattern within networks that may mediate the therapeutic effects of vagal input. The analysis was performed with IMaGES (Independent Multisample Greedy Equivalence Search) using the fMRI timecourse data of healthy participants who underwent non-

invasive vagus nerve stimulation. Using this approach on brain regions that respond to, and modulate, pain (e.g., periaqueductal gray, anterior cingulate, insula, thalamus, and somatosensory cortex), we found that vagal input shifts the connectivity pattern in a "bottom-up" direction (i.e.,, lower brainstem regions to forebrain regions) compared to rest. This pattern persists into the post-stimulation period, which is consistent with the persisting effects of vagal stimulation. This analysis can provide insight on the underlying mechanism of action of vagus nerve stimulation and a basis for comparison with patient populations responsive to vagus stimulation.

Disclosures: E. Frangos: None. **B.R. Komisaruk:** None.

Poster

807. Brain Machine Interface: Non-Invasive Approaches

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Title: Neurofeedback training improves decoding accuracy in MEG/SSVEF

Authors: *H. ORA[1,2], K. KANSAKU[1,2];
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Abstract: A decoded neurofeedback method was recently proposed to lead brain activity to a target state by using functional magnetic resonance imaging (Shibata, et al., 2011). Real-time magnetoencephalography (rtMEG) is an emerging neurofeedback technology that could potentially benefit multiple areas of basic and clinical neuroscience, and we have applied an rtMEG system to perform decoded neurofeedback training of the MEG/steady-state visual evoked field (SSVEF). Eight able-bodied participants (age 33.8 years old, 7 females) participated in this study. We first conducted an SSVEF task (pre-training SSVEF task). In the task, the visual stimuli were displayed on a screen in front of the participant, and consisted of a circular checkerboard patch on the left and a circular checkerboard patch on the right. The checkerboard

patches flickered at 5Hz (left) or 6Hz (right). They were asked to attend to the left, right, or middle of the screen in the SSVEF task. A 306-channel Elekta Neuromag MEG scanner was used (Elekta Oy, Helsinki, Finland). We then constructed a sparse multinomial logistic regression (SMLR) decoder from the MEG signals during the SSVEF task of each participant. After constructing the decoder, an MEG neurofeedback training was conducted to improve the decoding accuracy for either right or left orientation. The orientation that showed lower decoding accuracy was selected as a target. In the training, a white fixation cross at the center of the screen was turned green for 5 second, then a green solid circle, whose radius indicated the score of the SMLR decoder, was presented. Participants were asked to "somehow regulate your brain activity to make the green solid circle bigger while the fixation cross is green". During the training, any flickering visual stimuli were not presented. After the training, the SSVEF task was used again to evaluate the training effects (post-training SSVEF task). The experiment for each participant was performed in one day. In the pre-training SSVEF task to construct decoders, accuracy for the target orientation was significantly lower than that for the non-target orientation ($p<0.05$). In the post-training SSVEF task, accuracy for the target orientation and for the non-target orientation were not significantly different. The degree of improvement of accuracy for the target orientation was positively correlated with mean score of the SMLR decoder during training ($p<0.05$). The results suggest that the decoded neurofeedback training performed in one day was effective for MEG/SSVEF, and the method may be useful to enhance robustness of steady-state visual evoked potential-based Brain-Computer Interface.

Disclosures: H. Ora: None. **K. Kansaku:** None.

Poster

807. Brain Machine Interface: Non-Invasive Approaches

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: D.18. Brain-Machine Interface

Support: NIH NICHD Award PO1HD064653

Title: Neural development of social cognition in the first two years of life: Early findings from a cross-sectional study

Authors: *J. G. CRUZ-GARZA[1], Z. R. HERNANDEZ[1], M. MEGJHANI[1], B. ABIBULLAEV[1], T. W. TSE[2,3,4], E. CADUCOY[2], J. L. CONTRERAS-VIDAL[1,4];
[1]Electrical and Computer Engin., [2]Biol. and Biochem., [3]Mathematics, [4]Biomed. Engin., Univ. of Houston, Houston, TX

Abstract: Action understanding and action production are essential to developing socio-cognitive skills early in life. The neural basis of action understanding and the production of goal-oriented actions has been attributed to a postulated mirror neuron system (MNS) in human adults. However, little is known about the development of the MNS in human infants during unconstrained social interactions, in part due to the challenges associated with recording behavior and neural activity in freely behaving infants. To overcome these challenges, we propose a multi-modal neural decoding approach that integrates high-density scalp electroencephalography (EEG), inertial sensors and machine learning methods to study the emergence of the MNS in 6-24 month-old infants. Neural classifiers were trained to infer action intentions from time-domain features while the participants freely engaged in social interaction with an adult experimenter. EEG data was cleaned using Artifact Subspace Reconstruction (ASR), band-pass filtered in the delta (1 - 4 Hz) and alpha bands (6 - 9 Hz), and standardized. A neural classifier based on locality-preserving Fisher's discriminant analysis and Gaussian mixture models was deployed and cross-validated to infer behavioral output from scalp EEG in each infant. We applied the minimum Redundancy-Maximum Relevance (mRMR) algorithm to determine the channels relevant for classification of the behaviors displayed. Overall mean classification accuracies from a cohort of typically developing healthy infants (N= 9, age range = 6 - 23 months; 5 males/4 females) ranged from 59% - 95.5% (with 83.4% median accuracy), which was well above chance-level even when considering the number of classes used for classification. As expected, class number increased as a function of age from 3 at 6 months to 6 at 23 months, whereas imitation actions emerged around the age of 9 to 11 months. mRMR results showed that features most relevant to decoding included neural activity over fronto-central and posterior scalp areas occurring at lags 30 - 50 ms before movement onset attesting to their predictive nature. Overall, these findings show the feasibility of decoding behavior 'in action and context' during social interaction from noninvasively acquired delta and mu-band neural activity in freely behaving infants for the first two years of life. This research is supported by NIH NICHD Award PO1HD064653.

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Poster

807. Brain Machine Interface: Non-Invasive Approaches

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the Baden-Wuerttemberg Stiftung (ROB-1)

Title: Deciphering brain oscillations during motor rehabilitation tasks

Authors: *A. RAMOS MURGUIALDAY[1], N. BIRBAUMER[2];
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Abstract: Stroke non-invasive Brain-Computer-Interfaces (BCI) coupled with robotic exoskeletons were recently and successfully used in motor rehabilitation of chronic stroke patients (Ramos-Murguialday et al 2013). Motor rehabilitation involves several motor actions during training that could influence and may limit the use of BCIs for this purpose. We investigated the neurophysiological correlates of an EEG-oscillations-driven BCI combined with a robotic orthosis to define, if existing, the specific oscillatory signature of the proprioceptive BCI-task. Controlling movements of a hand robotic exoskeleton using motor imagery of the same movement generates sensorimotor rhythm oscillations due to motor components common to stroke motor rehabilitation: passive and active movement and motor imagery or motor intention. We recorded EEG while 9 healthy volunteers performed five different motor tasks consisting of closing and opening of the hand: 1) motor imagery without any feedback and without hand movement, 2) motor imagery based BCI, which moves the orthosis proportional to the produced brain oscillation change and provides online proprioceptive and visual feedback of the hand moving (BCI-condition, see Ramos-Murguialday et al 2012), 3) passive and 4) active movement of the hand with feedback (seeing and feeling the hand moving) and 5) rest. During the BCI-condition (2) participants received contingent on-line feedback of the decrease of power of the sensorimotor rhythm which induced orthosis movement and therefore proprioceptive and visual information from the moving hand. We analyzed brain activity using time-frequency domain bootstrap based statistical comparisons and Morlet transforms. Activity during rest was used as reference. Significant contralateral and ipsilateral decrease of sensorimotor rhythm power was present during all motor tasks, largest in contralateral-post-central, medio-central and ipsilateral-pre-central areas identifying the ipsilateral pre-central cortex as an integral part of motor regulation. We identified EEG features (spatial-time-frequency) representing active and passive motor oscillatory signatures differentiating brain oscillations during motor tasks that could substantially optimize the design of novel motor BCI-based rehabilitation therapies. Furthermore, the BCI task presented brain oscillatory signatures not present in the other motor tasks indicating neural processes unique to the use of body actuators control in a BCI-context.

Disclosures: **A. Ramos Murguialday:** None. **N. Birbaumer:** None.

Poster

807. Brain Machine Interface: Non-Invasive Approaches

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: D.18. Brain-Machine Interface

Title: Identification of the brain activity driving the lower muscles used during locomotion

Authors: ***S. TAKEDA**[1], S. KASUGA[2], J. USHIBA[3];
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Abstract: Corticospinal tract (CST) plays an important role for voluntary control of foot movements during locomotion. In severe stroke patients, the ability for voluntary control during locomotion is markedly impaired because their CST is damaged. However, there are few rehabilitation measures to restore CST function for such disability. Recently, Brain-Machine Interface (BMI) system for stroke upper-limb rehabilitation has received much attention as an expected technology to restore CST function. In this system, when BMI detects characteristic brain activities such as a change in sensorimotor rhythm, a prosthesis assists to move a patient's paralyzed hand. Such processes are considered to help regain normal neural activities and enhance CST excitability accompanying intent for upper-limb movements, through multiple learning mechanisms. Thus we hypothesized that BMI system to enhance CST excitability may also be applied to repair voluntary foot movements. However, features of brain activities reflecting intent for foot movements have yet to be identified. In the current study, we aimed at identifying an electroencephalogram (EEG) biomarker reflecting voluntary activation of the rectus femoris, which is the muscle mainly used for the starting of walking, in both healthy individuals and stroke patients. In addition, we validated if this biomarker reflected CST excitability by using Transcranial Magnetic Stimulation (TMS). One hundred and twenty nine channels of scalp EEGs were recorded during either motor execution (experiment 1) or imagery (experiment 2) of foot movements from thirteen healthy individuals and five stroke patients in total. In experiment 1, to identify the EEG biomarker of activation of the rectus femoris, healthy individuals and stroke patients were asked to execute either right hip flexion or ankle dorsiflexion as a control in a random order. Healthy individuals showed event-related desynchronization (ERD) in the beta band (20-30 Hz) over the motor cortex (Cz) during right hip

flexion, while stroke patients did not. In experiment 2, to test CST excitability during motor imagery, healthy individuals were asked to imagine right hip flexion. TMS was randomly applied to the hotspot of right rectus femoris during imagery. We found that motor evoked potential induced by TMS was positively correlated with magnitude of beta ERD at Cz. These findings suggest that BMI training to modulate beta ERD in the motor cortex may help increase excitability of CST connecting to the rectus femoris, and improve voluntary control of foot movements in severe stroke patients.

Disclosures: **S. Takeda:** None. **S. Kasuga:** None. **J. Ushiba:** None.

Poster

807. Brain Machine Interface: Non-Invasive Approaches

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Topic: D.18. Brain-Machine Interface

Support: Endowment funds of Harvey F. Brush

Paul and Harriet Campbell Fund for ALS Research

ALS Association Greater Philadelphia Chapter

Title: Amyotrophic lateral sclerosis and cognitive impairment alter optimal features for brain-computer interfaces

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Abstract: Brain-computer interfaces offer persons with amyotrophic lateral sclerosis (ALS) alternative means of communication. We identify ways in which personalization of feature selection benefits users on an individual level, and describe trends in optimal features that emerge when taking into account cognitive impairment, a major predictor of BCI performance. Twenty five patients with ALS and fifteen neurologically healthy control participants completed four sessions of electroencephalography-based brain-computer interface training with P300 and motor-imagery tasks. Participants were also given a cognitive screen to assess for possible cognitive impairment. Exhaustive optimization was carried out on the features produced during these sessions to identify the optimal spatiotemporal set of classification features for each

individual. Additionally, alternative task features of coherence, describing functional network connectivity, were assessed for classification utility in these groups. P300 feature space differed for controls and ALS patients as a whole. In controls, typical timing of task discriminable features occurred 300-400 ms after the visual stimulus, whereas time windows around 500 ms produced the lowest classification error in patients. ALS patients exhibited a wider distribution of P300 features in frontal electrodes, while in controls, discrimination between classes was exclusively found in centro-parietal regions. High performing users who produced lateralized power changes in response to motor imagery also displayed lateralized coherence changes. There were also individuals who demonstrated whole brain modulations of coherence which were hemisphere invariant and unassociated with changes in classical power features. There was a trend for the 14/25 patients with cognitive impairment to achieve better classification using coherence features than either cognitively normal patients or control participants. This study shows how the optimal features for BCI classification may change as a result of ALS as well as the cognitive impairment that often occurs with the disease. Effective use of BCI devices by individuals with ALS will rely on system personalization.

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Poster

807. Brain Machine Interface: Non-Invasive Approaches

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Support: EU TINNET COST Action BM1306 STSM Grant

Jenny and Antti Wihuri Foundation

Title: Combined transcranial alternating current stimulation (tACS) and MEG: tACS-induced reduction in the auditory steady-state response

Authors: ***P. HYVÄRINEN**[1], S. D. CHOI[2], G. DEMARCHI[2], A. A. AARNISALO[1], N. WEISZ[2];
[1]Univ. of Helsinki and Helsinki Univ. Hos, Helsinki, Finland; [2]Ctr. for Mind/Brain Sci., Univ. of Trento, Trento, Italy

Abstract: Transcranial alternating current stimulation (tACS) is a noninvasive method used to rhythmically stimulate the brain. By investigating neural activity patterns and behavioral

performance before and after stimulation, previous studies have shown that tACS can modulate and entrain ongoing brain oscillations. However, simultaneous measurement of brain activity during the application of tACS has not been performed until very recently by Neuling et al. (under review), who successfully measured changes in visual areas during tACS. In order to better understand the mechanisms through which tACS induces its effects on the brain, it is important to study ongoing brain activity during stimulation. Recording brain activity and concurrently applying tACS is challenging, since the electrical currents produced by the stimulator exceed the level of neural activity by many orders of magnitude. When conducting electrophysiological measurements with electroencephalography (EEG) or magnetoencephalography (MEG), these stimulator currents manifest as major artifacts in the measured data. Artifacts hinder the analysis of genuine brain activity during stimulation, especially when working with the data in time-domain. Although beamforming suppresses the highly coherent artifacts remarkably and allows tracking changes in source-level activity, one can also use sinusoidal stimulating currents and inspect the measured data in the frequency domain where artifacts are limited to narrow peaks around multiples of the stimulating frequency. Thus, by choosing the frequency of sinusoidal tACS suitably, one can investigate brain activity in the frequency bands between artifact peaks. We measured the auditory steady-state response (ASSR) to a 41-Hz click train with MEG, both during sinusoidal 12-Hz tACS and without tACS. 18 healthy volunteer subjects participated in the experiment. tACS was applied through two saline-soaked 35 cm2 electrodes bilaterally over the temporal lobes, targeting the auditory cortices. We estimated source-level activity using an LCMV beamformer. A comparison of tACS and no-tACS conditions revealed a significant tACS-induced reduction in the ASSR in the right auditory cortex. This study is the first to simultaneously combine auditory MEG measurements with tACS. The study also demonstrates for the first time the real-time effects of tACS on ongoing auditory brain activity. The method described here can be applied to other sensory modalities as well as to clinical resting-state measurements.

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Poster

807. Brain Machine Interface: Non-Invasive Approaches

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Program#/Poster#: 807.26/V48

Topic: D.18. Brain-Machine Interface

Title: Development of an unsupervised and multiclass steady-state visual evoked potential based - BCI

Authors: *K. IKEMOTO, Y. ONO;
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Abstract: In order to facilitate the use of steady-state visual evoked potential (SSVEP) based brain-computer interface (BCI) as an easy-to-use assist device for the physically challenged people, we have previously proposed the unsupervised multi-class classification algorithm of SSVEP-BCI, which uses features both from spectrum power of raw EEG data and from averaged EEG signals. Our previously proposed algorithm adopts spectrum power in case that signal-to-noise ratio of the spectrum power is large enough, and otherwise adopts average EEG signals. The classification using spectrum power detects the frequency which gives the maximum peak-to-baseline amplitude of the spectrum power among the frequency bands corresponding to the flicker light stimuli. The classification using averaged EEG signals detects the frequency which gives the maximum peak-to-peak amplitude of visual evoked potential by dividing and averaging the raw EEG data with different cycles corresponding to the flicker frequencies. Both methods are applied to the data at each electrode (O1, O2, Oz) and majority voting among the results at three electrodes determines the final output of the classifier. To further increase the accuracy, we examined whether (1) a spectrum feature that incorporates the peak-to-baseline amplitude of the spectrum power at the harmonic frequencies of the flicker frequency in addition to those at the fundamental frequency, and/or (2) a winner-take-all fashion of classification in both algorithms depending on spectrum power and averaged EEG signals (classification based on the feature at a single electrode showing the maximum peak-to-baseline or peak-to-peak amplitude among three electrodes), could improve the accuracy of the classifier. The best accuracy (81.3%, N=32) was obtained when we incorporated the peak-to-baseline amplitude at the first and the second harmonics into features and selected the frequency at which the peak-to-baseline or peak-to-peak amplitude showed the largest value among the stimuli frequencies and electrodes. With this improved feature selection and classification algorithm, we could significantly improve the accuracy of the classifier compared to our previous algorithm (77.0%, $p<0.01$).

Disclosures: **K. Ikemoto:** None. **Y. Ono:** None.

Poster

807. Brain Machine Interface: Non-Invasive Approaches

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Topic: D.18. Brain-Machine Interface

Support: Gigtforeningen R123-A3175

Title: Chronic musculoskeletal pain and its effects on brain activation

Authors: B. D. EBBESEN, J. RASMUSSEN, S. GERVASIO, T. GRAVEN-NIELSEN, *N. MRACHACZ-KERSTING;
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Abstract: Neurofeedback methods have a significant potential to reverse the maladaptive brain plasticity associated with pain conditions. Neurofeedback has been implemented for central neuropathic pain or migraines, while the patient is at rest or imagining a movement. Patients are trained to control specific waves (recorded using non-invasive electroencephalography - EEG) thereby reducing the pain. No current data is available for its potential use in the treatment of musculoskeletal pain. Since in these conditions, pain interacts with movement performance the initial aim of this study was to establish EEG signatures of chronic musculoskeletal pain (Lateral Epicondylalgia (LE)) and experimentally induced pain when a volunteer performs a movement. Pain patients with LE (n=6, age 46±10.7 years, 1 male) and healthy controls (n=6, age 26.5±6.2 years, 1 male) were asked to perform 30 repetitions of 3 movement tasks: index finger lift, grip force, and wrist extension. Continuous EEG (250 Hz sample rate) was measured from C3, F3, FC5, FC1, T7, Cz, CP5, CP1, and P3 and electromyographic (EMG) activity was recorded from the extensor carpi radialis brevis muscle. For each trial, EEG segments (+/- 2 s from EMG onset), were extracted and divided into preparation and execution phases. The power spectra within the alpha, beta, theta and gamma frequencies were extracted and compared between groups. The participants' subjective pain sensation was assessed on a visual analogue scale (VAS), pressure pain thresholds (PPT), and pain questionnaires. Compared with healthy controls, pain patients, as well as subjects with hypertonic saline injections compared with baseline showed an increased power of the alpha band in both the preparation (-0.4 to -0.05s) and execution phase (-0.05 to 0s). For the index finger task the mean difference was 8.2 Hz for preparation and 7.7 Hz for execution ($P<0.05$). Similar tendencies were seen for the other tasks. This was correlated to the VAS score ($R^2=0.62$ for the preparation phase and $R^2=0.61$ for the execution phase). Previous studies have demonstrated a decrease in alpha and increase in beta band power following saline-induced pain. In this pilot study the opposite trend was found for EEG monitored during movement execution. Results corroborate that pain interacts with movement performance and that this has an EEG signature. In addition, injection of hypertonic saline is further validated as an appropriate model to mimic musculoskeletal pain since the alterations in band power frequency followed the same trend as in chronic pain patients. The results will be a platform for full scale studies of neurofeedback techniques to manage chronic musculoskeletal pain.

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Poster

808. Neural Control of Respiratory Rhythm

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Topic: D.20. Respiratory Regulation

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Title: A novel model of respiratory rhythm generation: a mechanism by interaction of intrinsically oscillating astrocytes and neurons

Authors: *Y. OKADA[1], Y. OKU[2], T. SASAKI[3], C. VIVAR[4], S. YOKOTA[5], K. TAKEDA[1,6], I. FUKUSHI[1,7], I. YAZAWA[8], H. SOMEYA[9], Y. TAMURA[10];
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Abstract: A number of theories to explain the mechanism of respiratory rhythm generation have been proposed, e.g., a pacemaker theory in which pacemaker neurons initiate inspiration and a network theory in which respiratory rhythm is generated by interaction of excitatory and inhibitory neurons. However, respiratory rhythm could persist under blockade of pacemaker currents or inhibitory synaptic transmission, suggesting that another mechanism is involved. Recently, we have discovered that a subset of astrocytes show periodic activation preceding inspiration in the pre-Bötzinger complex (preBötC) in medullary slices (Okada et al. 2012; Oku et al. 2015). These preinspiratory astrocytes have an intrinsic oscillatory property, although they

receive excitatory drive from neurons. We confirmed that astrocytes and neurons are anatomically closely coupled in the preBötC, collectively suggesting that inspiration could be triggered by interaction of astrocytes and neurons. Indeed, blockade of astrocytic metabolism which depletes glutamate in neurons suppresses respiratory rhythm. However, substitution of glutamine restores the rhythm. Further, respiration of spontaneously breathing animals is generally much faster than intrinsic oscillatory rhythm of astrocytes. Therefore, we could not simply conclude that every inspiration is triggered by astrocytes. Here we propose a model to explain the mechanism of respiratory rhythm generation under *in vitro* and *in vivo* conditions. In the respiratory center, rhythmogenic astrocytes and neurons, both of which could have intrinsic oscillatory properties and could be sources of tonic excitatory drive as well, are mutually coupled through astrocyte-astrocyte, astrocyte-neuron and neuron-neuron synapses. They are periodically and synchronously activated, and can together trigger inspiratory activities of downstream neurons. Astrocytes also modulate neuronal activity by buffering various ions and transmitters in the extracellular space. The nature of small-world network connectivity among astrocytes as well as chaotic characteristics of astrocytic activity could be the basis of irregularity and robustness of respiratory rhythm. In normal conditions, astrocytes are involved in respiratory rhythmogenesis and modulate neuronal oscillator's rhythm. However, in some pathological conditions, astrocytes could primarily trigger inspiration at a low oscillatory frequency. When astrocytic activity is inhibited, neurons alone could form an oscillator and trigger inspiration if sufficiently boosted. This astrocyte neuron network model of respiratory rhythm generation explains the previous observations.

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Poster

808. Neural Control of Respiratory Rhythm

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 808.02/W3

Topic: D.20. Respiratory Regulation

Support: NIH Grant HL40959

Title: Neuromodulation of burst and burstlet rhythm generating mechanisms in preBötzinger complex (preBötC)

Authors: *X. SUN[1], K. KAM[2], M. SHAO[1], J. L. FELDMAN[1];
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Abstract: The preBötC is essential for generation of respiratory rhythm. *In vitro* in rhythmic slices from neonatal mice (P0-P5), preBötC population activity consists of two separable components: small amplitude rhythmic burstlets that represent preinspiratory activity and that we hypothesize are rhythmogenic, and larger inspiratory bursts, threshold triggered by burstlets, that drive inspiratory motoneuronal activity (Kam et al., J. Neurosci. 2013). Our hypothesis predicts that perturbations that modulate burst frequency (*f*) will also similarly affect burstlet *f* and that modulating excitability can separately affect the ratio of burstlets to bursts. When bathed in ACSF at 3 mM K^+ and 1mM Ca^{2+}, preBötC activity was a mixed pattern of burstlets and bursts. Increasing K^+ to 9 mM or the addition of the neurokinin receptor agonist Substance P (SP, 500nM) did not significantly affect *f* while significantly increasing the ratio of bursts/burstlets, whereas Cd^{2+} (<50 μM) decreased the ratio of bursts/burstlets. In contrast, the μOR agonist DAMGO (30-100 nM) decreased both burst and burstlet *f* and decreased the ratio of bursts/burstlets. The depressant effects of DAMGO were reduced by high K^+ and SP. We suggest that perturbations in preBötC neuronal excitability can alter the threshold for conversion of burstlets into bursts and that changes in *f* are reflected in changes to burstlet *f*. These data are consistent with distinct rhythm and pattern generating mechanisms within the preBötC, with rhythmogenesis being mediated by burstlets and a separable burst-generating mechanism being necessary for patterned output from the preBötC. Supported by NIH Grant HL40959.

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Poster

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NHMRC GNT1052674

Title: Regulation of breathing by carbon dioxide requires expression of the proton-activated receptor GPR4 in chemosensory neurons of the retrotrapezoid nucleus

Authors: *N. N. KUMAR[1], A. VELIC[2], J. SOLIZ[3,4], Y. SHI[1], K. LI[1], S. WANG[1], J. L. WEAVER[1], J. SEN[1], S. B. G. ABBOTT[1,5,6], R. M. LAZARENKO[1], M.-G. LUDWIG[7], N. MOHEBBI[2], C. BETTONI[2], M. GASSMAN[3], T. SUPLY[7], K. SEUWEN[7], P. G. GUYENET[1], C. A. WAGNER[2], D. A. BAYLISS[1];
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Abstract: BACKGROUND: Blood gas and tissue pH regulation depend on the ability of the brain to sense CO2 and/or H+ and alter breathing appropriately. A specific group of neurons within the medullary retrotrapezoid nucleus (RTN), identified by Phox2b expression, are preeminent central respiratory chemosensory neurons, i.e., they directly sense CO2/H+ and adjust ventilation to rapidly regulate CO2 excretion and acid-base balance. However, the molecular mechanisms that mediate pH sensing within RTN neurons remain incompletely understood. Recent work from knockout mice suggests that the alkaline-activated TASK-2 (K2P5) background K+ channels account for pH-sensitivity in a subset of RTN neurons but also implied that other molecular sensors must also play a role. In insects, CO2 sensing involves G protein-coupled receptors (GPCRs). Interestingly, a group of proton-activated GPCRs has been identified in mammalian systems, although their specific physiological roles remain to be elucidated. OBJECTIVE & METHOD: Here, we use a combination of genetic loss-of-function, cellular pharmacology and molecular biology, *in vitro* and *in vivo* physiology, and RTN neuron-specific lentiviral re-expression and rescue, in order to identify GPR4, a proton-activated G protein-coupled receptor, as a molecular substrate for CO2/H+-dependent RTN neuronal excitability and breathing. RESULTS: In mice lacking GPR4, the enhanced breathing induced by raised CO2 was strongly reduced, and these mice were also more prone to apneic events. Mice lacking GPR4 showed a striking reduction in CO2 induced activation of RTN neurons *in vivo*, as determined by cFos expression. Likewise, RTN neuronal excitability and pH sensitivity *in vitro* were reduced by GPR4 deletion or receptor blockade, and modulated by intracellular application of GTP analogs. Finally, virally-mediated re-introduction of GPR4 into RTN neurons of GPR4-/- mice rescued CO2-stimulated cFos expression and ventilation, and returned apneic frequencies to wild type levels. Additional deletion of TASK-2, a pH-sensitive K+ channel expressed in RTN neurons, essentially abolished the ventilatory response to CO2 in double knockout mice. CONCLUSION: Taken together, these data identify GPR4 and TASK-2 as distinct, parallel and essential central mediators of respiratory chemosensitivity, and suggest new therapeutic options to regulate breathing.

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Poster

808. Neural Control of Respiratory Rhythm

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Topic: D.20. Respiratory Regulation

Support: NIH/NINDS R01 NS069220

Title: Mixed-mode oscillations and development of population bursts in the pre-Bötzinger complex

Authors: *B. BACAK[1], T. KIM[1], J. E. RUBIN[2], J. C. SMITH[3], I. A. RYBAK[1];
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Abstract: Generation of rhythmic activities in neural structures, representing central pattern generators, involves complex dynamic synchronization of neuronal activity in large populations of neurons with endogenous bursting properties. Our theoretical and computational study focused on population activity that developed progressively with elevation of neuronal excitability in the pre-Bötzinger complex (pre-BötC), a medullary region known to be critically involved in the generation of the inspiratory phase of respiration. Progressive increase in extracellular potassium concentration in medullary slices containing the pre-BötC produces complex mixed-mode oscillations, characterized by amplitude modulation with large population bursts alternating with a series of small bursts (so-called “burstlets”). When the network’s excitability, which correlates with extracellular potassium concentration, is sufficiently high, only large amplitude bursts are observed. To study the generation of, and the relations between,

bursts and burstlets, we developed and analyzed two models: (a) a computational model of a network of 100 neurons, described in the Hodgkin-Huxley style, with bursting properties defined by the persistent (slowly inactivating) sodium current (INaP), sparse excitatory synaptic interconnections, and randomly distributed neuronal parameters, and (b) a reduced model consisting of three mutually exciting non-spiking neurons that allowed us to apply qualitative analytical methods for understanding key system behaviors. We show that the mixed-mode oscillations observed in the pre-BötC and similar systems can emerge within a single heterogeneous network due to recruitment and synchronization of multiple neurons involved in the generation of both bursts and burstlets. The resultant pattern of these mixed-mode oscillations depends on the distribution of neuronal excitability, sparsity and weights of network connections, and the neuronal properties underlying endogenous bursting (e.g., INaP). The latter should specifically provide a reduction of spiking activity within neuronal bursts with increasing burst frequency and a dependence of the after-burst recovery period on the burst amplitude. We conclude that the generation of mixed-mode oscillations observed in the pre-BötC *in vitro* does not require distinct sub-networks for rhythm generation and pattern formation.

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Poster

808. Neural Control of Respiratory Rhythm

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: D.20. Respiratory Regulation

Title: Neuronal TRPC3/7 channels play a critical role in breathing rhythm generation *in vivo*

Authors: *A. K. TRYBA;
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Abstract: The mechanisms underlying disordered breathing patterns are poorly understood. The neural mechanisms that govern respiratory rhythm generation, including the cellular/ionic mechanisms and specific neurons of the respiratory control center are also not fully known. The pre-Botzinger Complex (Pre-BotC) is a brainstem region hypothesized to be an essential component of the respiratory network, playing a critical role in generating normal inspiratory breathing rhythms. Both *in vitro* (Ben-Mabrouk and Tryba, 2010; Ben-Mabrouk et al. 2012) and *in situ* experiments were used to start to identify ion channel targets that modify the bursting properties of pre-BötC neurons, including transient receptor potential (TRPC) channels. These

studies suggested that glutamatergic synaptic drive together with excitatory neuromodulators can activate TRPC3 and/or TRPC7 (TRPC3/7) channels to enhance inspiratory neuron bursting properties and stabilize inspiratory rhythms. Using *in vitro* brain slice preparations containing the pre-BotC, I made intracellular recordings dialyzing pre-BotC inspiratory neurons with selective TRPC3/7 antibodies, which reduced the inspiratory neuron drive potential (n=4), indicating that TRPC3/7 channel activation enhances inspiratory neuron bursting properties. In a novel approach to begin to define the role of TRPC3/7 channels in breathing pre-BotC *in vivo*, I stereotaxically injected a modified siRNA to selectively knock down expression of TRPC3 and TRPC7 channels in pre-BötC neurons of rats *in vivo*. I monitored rats' breathing using flow-through plethysmography and sleep/wake states using EEGs. Selectively interfering with TRPC3/7 protein production in neurons in the pre-BotC region results in repetitive sleep apnea, suggesting that TRPC3/7 channels play a critical role in breathing rhythm generation *in vivo* and that reduced availability of TRPC3/7 cannot be compensated for over several (~7) days of the study (n=7/7). In contrast, stereotaxic injection of non-targeting control siRNA sequences into the pre-BotC did not result in sleep apnea or other significant changes in breathing (n=7/7). For the first time, these data suggest that activation of TRPC3/7 channels in pre-BotC neurons plays an critical role in breathing, particularly during sleep. These data are also of interest, given that circulating levels of excitatory neuromodulators (e.g., Substance P, 5-HT) that can activate these channels are low during sleep and it appears that the respiratory system cannot compensate for selective reduction in availability of TRPC3/7 channels at that time. Enhancing TRPC3/7 in pre-BotC neurons may prevent disordered breathing.

Disclosures: A.K. Tryba: None.

Poster

808. Neural Control of Respiratory Rhythm

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Topic: D.20. Respiratory Regulation

Support: NIHGMS GM48677

Title: Combining constellation pharmacology with molecular genetics to classify neuronal cell types within the ventral respiratory column of mouse brainstem

Authors: *S. RAGHURAMAN[1], A. GARCIA[2], R. TEICHERT[1], J. RAMIREZ[2], B. OLIVERA[1];

[1]Dept. of Biol., Univ. of Utah, Salt Lake City, UT; [2]Ctr. for integrative brain research, Seattle Children's Res. Inst., Seattle, WA

Abstract: Constellation pharmacology is a methodology to identify and classify different neuronal cell types based on the sets (or constellations) of ion channels and receptors found in every cell type. We performed constellation pharmacology through calcium imaging to classify three major cell classes and subclasses within the ventral respiratory column (VRC) of mouse brainstem. Previous results published on these cell classes examined and confirmed that the cellular response profiles in an intact slice exhibited similar responsiveness as was found *in vitro* [1]. To further understand the physiological roles of these identified cell types, we performed constellation pharmacology on two different types of transgenic reporter mice that expressed tdTomato in genetically defined neuronal cell types. The cholinergic and glutamatergic neurons of VRC were labeled with tdTomato, with expression driven by promoters of the genes encoding choline acetyltransferase (ChAT) and the transcription factor Dbx1 respectively. Our results demonstrate that these cholinergic and glutamatergic cell types were a subset of our defined cell classes within VRC, thereby strengthening our classification. To further refine the definition of these cell classes, we used target-selective conotoxins that differentiated between complex molecular isoforms. For example, NMDA receptors that are found in various combinations of subunits are difficult to study due to the lack of target selective tools. Using conantokin-Rl-B, a peptide that selectively targets NR2B subunits of NMDA receptors, we identified its expression only in a specific subset of the defined cell types. Thus, this approach of combining constellation pharmacology with molecular genetics has provided a platform to classify cell types with crucial physiological roles in behavior and to generate hypotheses to test the roles of modulatory inputs to these defined cell classes in an intact system. Reference: [1] Raghuraman S, Garcia AJ, Anderson TM, Twede VD, Curtice KJ, Chase K, Ramirez JM, Olivera BM, Teichert RW. Defining modulatory inputs into CNS neuronal subclasses by functional pharmacological profiling. PNAS (2014). 111(17): 6449-54

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Poster

808. Neural Control of Respiratory Rhythm

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Topic: D.20. Respiratory Regulation

Support: Intramural Research Program of NINDS, NIH

Title: Optogenetic studies of population-specific roles of pre-Bötzinger complex glutamatergic neurons in respiratory rhythm generation

Authors: *H. KOIZUMI, M. TARIQ, B. MOSHER, R. ZHANG, N. KOSHIYA, J. C. SMITH; Cell. & Systems Neurobio. Sec, NINDS, NIH, Bethesda, MD

Abstract: The rhythm of breathing in mammals is generated within the pre-Bötzinger complex (pre-BötC), a circumscribed and functionally-specialized region of the ventrolateral medulla, involving cellular and circuit mechanisms that are not fully defined despite over two decades of investigation. The pre-BötC has a heterogeneous composition of rhythmically active excitatory and inhibitory interneurons, and it is generally assumed that glutamatergic neurons constitute the rhythmogenic kernel for inspiration. However, it has not yet been possible to directly demonstrate such causality in rhythm generation without methods to specifically manipulate activity of pre-BötC glutamatergic neurons. We now demonstrate this causality by leveraging optogentics with transgenic mice expressing Cre-recombinase in glutamatergic neurons promoted by the vesicular glutamate transporter 2 (VGLUT2) for conditional cell-type specific expression of Archaerhodopsin-3 (Arch, light driven outward proton pump) in neonatal medullary slices *in vitro* and in the functionally more intact juvenile/adult perfused brainstem-spinal cord preparations *in situ*. In these VGLUT2-Arch mice, optogenetic attenuation and loss of function of pre-BötC glutamatergic neurons caused rapid and reversible disruption of inspiratory rhythm generation in a site-specific manner. We further analyzed, by whole-cell patch-clamp recordings, the relationship between the laser-induced (2-10 mW) neuronal membrane hyperpolarization of functionally identified glutamatergic pre-BötC inspiratory neurons vs. the frequency of inspiratory bursting activity generated in medullary slice preparations *in vitro*. The results showed a monotonic reduction of inspiratory burst frequency as a function of membrane hyperpolarization, consistent with a membrane voltage-dependent mechanism underlying inspiratory rhythmogenesis. These results provide a more definitive demonstration of the molecular/neurotransmitter phenotype specification of the essential rhythmogenic neurons in the pre-BötC.

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Poster

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Parker B. Francis Fellowship

Dunn Collaborative Research Award

Title: Functional mapping of genetically-defined neuron populations in central control of respiratory physiology

Authors: *J. SUN, R. RAY;
Neurosci., Baylor Col. of Med., Houston, TX

Abstract: The perpetual rhythm of breathing is essential for survival and emerges through the interactions of a highly redundant and anatomically complex array of neuronal networks. As a result, central respiratory circuits are challenging to study, and the underlying causes of congenital respiratory disorders and diseases including Rett Syndrome, Congenital Central Hypoventilation Syndrome, and Sudden Infant Death Syndrome remain unclear. A necessary step toward diagnosis and treatment of respiratory dysfunction is identifying the roles of specific populations of neurons within the central respiratory circuitry. Here we use acute, non-invasive, and reversible pharmaco-genetic methods to precisely perturb (hM4D) and stimulate (hM3D) genetically-defined developmental and neurotransmitter-based populations in the adult mouse brainstem. hM4D and hM3D are modified G-protein coupled receptors that are biologically inert until activated by administration of the synthetic ligand clozapine-N-oxide (CNO), which causes neuronal silencing via hyperpolarization or stimulation via burst firing, respectively. By expressing these receptors in a conditional Cre and/or FLP recombinase-responsive manner, we can target widely-dispersed and developmentally critical populations, resulting in high spatial resolution and bypassing embryonic or neonatal lethality. In combination with whole-body plethysmography, we are able to accurately measure respiratory parameters under room air, hypercapnic (5% CO_2), and hypoxic (10% O_2) conditions in conscious and unrestrained mice. Our data demonstrate that genetically defined segments of the developing hindbrain called rhombomeres contribute to the functional organization of the adult respiratory network, differentially affecting respiratory rate, tidal volume, oxygen consumption, and waveform patterns when they are perturbed or stimulated under different breathing conditions. We also show that neurotransmitter expression defines populations with distinct respiratory roles. Together, these data set the stage for intersectional mapping of dual-gene expressing subpopulations to further refine neuron subtypes involved in respiratory homeostasis and expand our understanding of the intricacies of central respiratory circuits.

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Poster

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Topic: D.20. Respiratory Regulation

Support: NIH grant RO1NS19814

Title: Medullary raphé neuron responses during central chemoreceptor perturbations and functional connectivity within the respiratory brain stem

Authors: K. E. ICEMAN, S. C. NUDING, L. S. SEGERS, *B. G. LINDSEY, K. F. MORRIS; Dept. of Mol. Pharmacol. & Physiol., Univ. of South Florida Morsani Col. of Med., Tampa, FL

Abstract: Different classes of medullary raphé neurons are hypothesized to function as sensors of central CO_2: mildly CO_2-stimulated serotonergic (5-HT) neurons, robustly CO_2-stimulated non-serotonergic neurons, and inhibitory neurons that are themselves CO_2-inibited. These raphé neurons are proposed to function together in a "push-pull" manner to enhance breathing during central chemoreceptor stimulation via excitation and disinhibition of target neurons within the raphé and other brainstem respiratory regions. To address the hypothesis that CO_2-responsive raphé neurons form such functional connections, we used multi-array recording and cross-correlation methods to evaluate spike train data from the medullary raphé nuclei, ventral respiratory column (VRC), and pontine respiratory group of 6 decerebrate, vagotomized, neuromuscularly-blocked cats. Phrenic activity, blood pressure, end-tidal CO_2, and arterial blood gas measures of O_2, CO_2 and pH were monitored. Thirty-nine percent (26/67) of the raphé neurons recorded changed firing frequency during selective stimulation of central chemoreceptors (injection of CO_2 saturated saline via vertebral artery). When the 26 neurons were tested with hypocapnia induced by hyperventilation, 46% (12/26) had a response opposite to the injections, 46% (12/26) had no response, and 8% (2/26) had the same response. Offset peak and trough features in correlograms triggered by raphé neurons with target cells in the raphé, VRC, and pons support a "push-pull" model: CO_2-stimulated and CO_2-inibited raphé neurons excite and disinhibit target neurons, respectively. The results support the hypothesis that chemoresponsive raphé neurons modulate respiratory drive during conditions of altered CO_2 via local circuits within the raphé and through parallel connectivity with the VRC and pons.

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Poster

808. Neural Control of Respiratory Rhythm

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Topic: D.20. Respiratory Regulation

Support: NIH Grant HL122921

NIH Grant HL095731

Title: Optogenetic activation of leptin-receptor expressing NTS neurons increases respiratory motor output in mice

Authors: Z. CHANG, A. S. KOWAL, G. SEKERKOVA, K. E. MCKENNA, M. MARTINA, *D. R. MCCRIMMON;
Dept Physiol., Northwestern Univ. Feinberg Schl Med., Chicago, IL

Abstract: Administration of the anorexigenic hormone leptin to rodents increases energy expenditure with a parallel increase in respiratory motor output so that arterial blood gas and acid-base balance are maintained. This occurs at least in part through activation of CNS neurons that express the long form of the leptin receptor (LepRb). LepRb expressing neurons are concentrated in several CNS regions, most notably in the hypothalamus and brainstem. Of these, activation of LepRb neurons in the nucleus of the solitary tract (NTS) has been linked to respiratory motor stimulation. We have initiated studies to characterize the NTS LepRb neurons contributing to respiratory stimulation using mice that express channelrhodopsin-2 (ChR2) in LepRb neurons. Mice were anesthetized and a optical fiber (200-300 um diameter) conducting 473 nm wavelength light was used to activate the ChR2-LepRb neurons. Light intensity was maintained below 3 mW to avoid nonspecific activation or damage to tissue in the vicinity of the fiber. For stimulation, trains of light pulses at 5, 10, 20 and 50 Hz (≤10 ms pulse width) were used. In parallel control experiments in mice not expressing LepRb-ChR2, these stimulus parameters did not elicit any change in respiratory motor output. In contrast, when the NTS region of mice expressing ChR2 in LepRb neurons was optogenetically activated, there was a progressive increase in respiratory motor output, consisting primarily of an increase in the peak amplitude of integrated phrenic nerve activity with little change in the number of phrenic bursts per minute. The magnitude of the increase in the peak amplitude of phrenic nerve bursts was

directly dependent on the stimulus frequency, with a maximum of about a doubling in amplitude. Current studies are using retrograde tracing and immunohistochemistry to identify candidate neurotransmitters within NTS LepRb neurons that project to neurons within brainstem regions that contain respiratory neurons. We are grateful for the support from NIH grants HL122921 and HL095731.

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Poster

808. Neural Control of Respiratory Rhythm

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Topic: D.20. Respiratory Regulation

Support: FONDECYT #1130874

CONICYT fellows Training Program for Advanced Human Capital

Title: Perinatal fluoxetine exposure affects the serotonergic drive of the respiratory rhythm *in vitro*

Authors: *K. A. BRAVO[1], J. EUGENÍN[2], I. LLONA[1];
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Abstract: Serotonin (5HT) is a proliferation and differentiation factor at gestational period, being 5HTergic maternal tone important for overall embryonic brain development (Bonnin and Levitt Neuroscience 197(2011)1-7; Neuropsychopharmacol 37(2012)299-300). Administration of selective inhibitors of 5HT reuptake during pregnancy alters 5HT levels, which we propose may lead to modification of neural circuitry with functional effects on central chemosensory responses (Alwan and Friedman CNS Drugs 23(2009)493-509). We previously found that, at the postnatal day 8 (P8), perinatal fluoxetine exposure decreased: 1) the ventilatory responses to hypercapnia, 2) the recruitment of neurons expressing c-Fos induced by hypercapnia at the raphe and NTS nuclei, and 3) the respiratory response induced by hypercapnic acidosis in medullary slices. In the present work we extend our study to other postnatal ages and we investigated the effect of perinatal fluoxetine on 5HTergic drive on respiratory network. Osmotic minipumps were implanted to CF-1 dams on day 5 of pregnancy, to deliver fluoxetine (7mg Kg-1 day-1) for up to 28 days. Plethysmographic head-out recordings were done in adults (P40) mice breathing

either air or air enriched with 10% CO2. Fictive respiratory activity was recorded from ventral respiratory column with suction electrodes and exogenous 5HT was delivered by superfusion, and respiratory frequency was evaluated by concentration-response curve. Fluoxetine exposure reduced the ventilatory response to hypercapnia from P8 to adulthood (P40). Prenatal fluoxetine reduced the maximal response to exogenous 5HT observed in concentration-response curves in P8 medullary slices. Our results indicate that perinatal fluoxetine exposure impairs chemosensory reflexes and it is associated to a reduction in the 5HTergic command during postnatal life.

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Poster

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Topic: D.20. Respiratory Regulation

Support: ANR12-BSV4-0011-01

Title: Pacemaker neurons in the respiratory network of embryonic mouse

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Abstract: Breathing is a rhythmic motor behavior that is generated and controlled by neuronal assemblages located in the hindbrain. One such network, the preBötzinger complex (preBötC), plays a prominent role in generating the inspiratory phase of respiration. The status of this network at the time of its functional emergence during embryonic development has been recently described, but nothing is presently known regarding the existence and functional characteristics of preBötC inspiratory neurons that express pacemaker properties. We have aimed, firstly, to investigate the presence and properties of pacemaker neurons at embryonic stages, and secondly, to examine their potential role in respiratory rhythm generation and modulation at prenatal stages. To this end we combined multi-cellular calcium imaging with electrophysiological recordings of individual neurons in transverse brainstem slices obtained from mouse embryos (from embryonic day (E) 16 to 18). Patch-clamp recordings (n = 71) revealed the existence of heterogeneous pacemaker properties underlying three types of discharge pattern (long-lasting plateau-like bursts, short lasting-bursts and a mixed activity phenoptype). The effects of

pharmacological treatments associated with computational modeling indicated that this heterogeneity relies on distinct combinations of membrane conductances. The non-specific calcium-activated current (ICAN) plays a prominent role in the long-lasting, plateau-like discharge while the shorter bursting-like pattern relies more on the persistent sodium current (INaP). Furthermore we found changes in the respective proportion of the different pacemaker types during embryonic development, with the plateau-like bursting pacemakers being predominant at E16 while the bursting-like pacemakers being more prevalent at E18. Accordingly, rhythmogenesis is more affected by ICAN blockade at early embryonic stages and by INaP blockade at later stages. In addition, exogenous application of known neuromodulators of the respiratory rhythm (Substance P, DAMGO) revealed an intrinsic sensitivity of embryonic pacemaker neurons to these substances. Taken together our results provide the first description of pacemaker bursting properties in embryonic preBötC neurons, establish a developmental maturation of pacemaker properties and suggest an important role of pacemaker neurons in generating and governing activity of the prenatal respiratory network.

Disclosures: **M. Thoby Brisson:** None. **M. Chevalier:** None. **N. Toporikova:** None.

Poster

809. Neuroinflammation: General

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 809.01/W14

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: Boehringer Ingelheim

Title: Warfarin increases glial inflammation in healthy adult mice

Authors: *D. L. FEINSTEIN, A. SITU, N. MARANGONI;
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Abstract: The commonly used anti-coagulant warfarin reduces clotting by inhibiting vitamin K recycling necessary for activation of gamma-glutamyl carboxylase (GGC), which carboxylates and activates clotting proteins. Since vitamin K and GGC have roles in other physiological processes including within the CNS, we tested the hypothesis that chronic treatment with warfarin would lead to alterations in indices of neuroinflammation. Adult healthy mice were treated with warfarin for up to 4 weeks, after which brain sections were examined for signs of inflammation, sulfatide content, and expression of genes relevant to vitamin K regulated processes. As a control, we compared the effects of warfarin to those of the anti-coagulant

dabigatran etexeliate (DE), which in contrast to warfarin does not reduce vitamin K levels but directly inhibits thrombin. Statistical comparisons were made by 1-way ANOVA and Student t-tests. We observed that after 4 weeks, warfarin, but not DE induced significant microglial and astroglial activation in different brain regions (cortex, cerebellum, and hippocampus) while in contrast DE showed trends towards reducing the basal levels of glial inflammation. Ultra HPLC analysis of samples measured after 1 week of treatment showed that warfarin, but not DE, reduced cerebellar levels of the C18:0 sulfatide. Quantitative PCR analysis showed that both warfarin and DE caused changes (both increases and decreases) in the expression of a panel of genes involved in vitamin K dependent processes, in different brain regions and with the largest changes in the cerebellum. These results suggest that warfarin, but no DE, induces alterations within the CNS including increased neuroinflammatory responses.

Disclosures: D.L. Feinstein: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Boehringer Ingelheim. **A. Situ:** None. **N. Marangoni:** None.

Poster

809. Neuroinflammation: General

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: AHA-14SDG18730034

Title: Temporal expression pattern of microglia/ macrophage polarization after intracerebral hemorrhage

Authors: *S. SUKUMARI RAMESH[1], F. C. BONSACK[2], C. H. ALLEYNE[2];
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Abstract: Intracerebral hemorrhage (ICH) is a fatal stroke subtype accounting for 15-20% of all strokes. Despite neurosurgical intervention and supportive care, the 30-day mortality rate remains 30-50%; with ICH survivors frequently displaying neurological impairments and requiring long-term assisted care. Notably, there is no effective treatment for ICH and the incidence of ICH is expected to grow over the next decades as a result of population aging and changes in racial demographics. Though, accumulating evidence demonstrates the role of neuroinflammation in secondary brain injury and delayed fatality after ICH, the phenotypic or functional characterization of microglia/macrophages, the cells that play key role in neuroinflammation, remains poorly defined after ICH. In the present study, ICH was induced in

CD1 male mice by collagenase injection method and immunofluorescence staining of brain sections for M1 and M2 markers was performed to characterize the phenotypic changes of microglia, 1 to 7 days post injury. Expression of M1 marker, CD16/32 was found to be increased in the peri-hematomal brain region 3 to 7 days post injury, peaking on day 5, in comparison to sham. In contrast, the expression of M2 marker, CD 206 was observed on post injury days 1 and 3 with a maximal expression on day 3. In addition, CD16/32 positive cells, remarkably co-localized with Iba1, indicating that the M1 marker expression is mainly confined to microglia/macrophages. Altogether, our results suggest the occurrence of an injury-induced dynamic shift of anti-inflammatory M2 to pro-inflammatory M1 microglia/macrophage after ICH and raise the possibility of targeting M1 microglia in ICH associated morbidity/mortality.

Disclosures: S. Sukumari Ramesh: None. **F.C. Bonsack:** None. **C.H. Alleyne:** None.

Poster

809. Neuroinflammation: General

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant GM060665

Title: PGJ2-induced Inflammation disrupts AMPA-receptor trafficking: implications for synaptic plasticity and memory processing

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Abstract: Inflammation has many detrimental effects on the nervous system, and can lead to cognitive impairment. However, little is known about the molecular mechanisms that underlie neuroinflammation-induced cognitive deficits. To address this gap in knowledge, we employed a cell-culture model of neuroinflammation in which rat E18 cerebral cortical cultures are treated with an endogenous neurotoxic product of inflammation, Prostaglandin J2 (PGJ2). Previous findings indicate that PGJ2 disrupts cellular homeostasis in neuronal cultures by decreasing protein turnover via a process that is regulated by the ubiquitin-proteasome system. Previous studies also show that spatial memory performance is positively correlated with the expression of the AMPA-receptor subunit GluA2 in the brain (Sebastian 2013 PLoS One. 8, e81121) and that

maintaining GluA2 levels within the synapse preserves a learned memory (Migues 2010 Nat. Neurosci. 13, 630-4). Thus, we hypothesize that inflammation could produce cognitive deficits by impairing the trafficking of GluA2 to and from the synapse. We performed immunocytochemistry on 10-DIV cortical-neurons and imaged neurons and their neurites by fluorescent microscopy. Images were quantitatively analyzed for levels of GluA2, PSD95 (a post-synaptic scaffolding protein), and their colocalization using ImageJ. Results showed that PGJ2 (1μM) significantly increased GluA2 and GluA2/PSD95 colocalization along neurites compared to controls. PSD95 levels were unchanged. Our results indicate that GluA2 levels increase at synapses after PGJ2 treatment due to a failure in their turnover that affects trafficking to and from the synapse. These results suggest that PGJ2 and inflammation have detrimental effects on synaptic homeostasis by disrupting protein turnover and blocking protein trafficking. Currently, our investigations are focusing on the mechanisms by which PGJ2 affects synaptic homeostasis, including the effects on protein kinase M zeta (PKMζ). This constitutively active enzyme is known to participate in the trafficking of GluA2 and is known to play a role in memory maintenance. These findings could explain why inflammation induces cognitive deficits.

Disclosures: **J.A. Avila:** None. **T. Jean-Louis:** None. **M. Kiprowska:** None. **F. Cheung:** None. **P. Rockwell:** None. **P.A. Serrano:** None. **M. Figueiredo-Pereira:** None.

Poster

809. Neuroinflammation: General

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Support: MC IRG 249274 to R.L-V

SAF2013-48431-R to R.L-V

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Title: Contribution of lysophosphatidic acid receptor 2 and 3 (LPA2 and LPA3) to secondary damage following spinal cord injury in mice

Authors: *E. S. NOGUEIRA[1], I. FRANCOS-QUIJORNA[2], M. COLL-MIRÓ[2], J.-P. SALLES[3], O. PEYRUCHAUD[4], J. CHUN[5], R. LÓPEZ-VALES[2];
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Abstract: Lysophosphatidic acid (LPA) is a pleiotropic extracellular lipid mediator with many physiological functions that signals through 6 known G protein-coupled receptors (LPA1-6). LPA1-3 share high homology in amino acid sequence and belong to the endothelial differentiation gene (edg) family LPA receptors, whereas LPA4-6 are genetically more distant and belong to the non-edg family LPA receptors. LPA mediates a wide range of LPA effects in the central nervous system, including neural progenitor cell physiology, astrocyte and microglia activation, neuronal cell death, and axonal retraction. Previous *in vivo* studies show that LPA is involved in the etiology of fetal hydrocephalus, as well as the development of neuropathic pain after sciatic nerve injury and cerebral ischemia. We previously reported that LPA plays an important role in the pathophysiology of spinal cord injury (SCI) by signaling through LPA1. Here we aimed at studying the contribution of the other two members of the edg family LPA receptors, LPA2 and LPA3, to secondary damage after SCI. We found that LPA2 and LPA3 mRNA levels are constitutively expressed in the spinal cord parenchyma and their transcripts are up-regulated after contusion injury. To dissect out the role of LPA2 and LPA3 in SCI, we induced contusion injury in LPA2 and LPA3 deficient mice. These experiments revealed that functional recovery, as well as myelin and neuronal sparing, was significantly enhanced in the absence of LPA2 signaling. The lack of LPA3, however, did not confer protection against functional deficits and tissue damage. Similarly, administration of OMPT, a LPA3 agonist, did not exert beneficial effects after SCI. To gain insight into the detrimental actions of LPA2 activation in spinal cord we performed *in vitro* studies. These experiments revealed that the detrimental actions of LPA2 signaling are mediated, in part, by activation of LPA2 in microglial cells. Overall, this study provide novel data demonstrating that LPA signaling via LPA2 contributes to tissue damage in SCI.

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Poster

809. Neuroinflammation: General

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIMH R21MH098181

NIMH R01MH100078

Title: Early life stress activates the innate immune system in the developing hippocampus

Authors: J.-C. DELPECH, L. WEI, J. HAO, R. K. LACHER, *A. KAFFMAN;
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Abstract: Exposure to childhood abuse and neglect is associated with an increase risk for the development of several behavioral, emotional, cognitive and medical sequelae. These psychiatric and medical comorbidities present early in life, and in many cases, persist into adulthood and are associated with enormous clinical and economical burden. The molecular and cellular mechanisms by which early life stress (ELS) causes such diverse and severe clinical outcomes is currently poorly understood in humans. Using a mouse model of ELS, known as brief daily separation (BDS), we recently showed that exposure to BDS is associated with impaired hippocampal dependent memory in adulthood, and abnormal synaptic maturation and pruning during the juvenile period. Given that microglia cells play a critical role in guiding normal synaptic maturation and synaptic pruning, we tested whether exposure to BDS alters microglia function in the developing hippocampus. To test this hypothesis we collected microglia from the hippocampus of 14-day old (during the BDS period) and in 28-day old pups (one week after the last day of BDS). We found that BDS increased the number and modified the morphology of microglia in 14-day old but not 28-day old pups. We then examined the effect of BDS on gene expression in microglia harvested from the hippocampus of 14-day old BDS and control pups. Path analysis indicated that BDS activates many genes involved in phagocytosis, cell cycle regulation, and immune activation. These findings demonstrate that exposure to BDS causes a dramatic shift towards a phagocytic transcriptional programming in microglia cells present in the developing hippocampus. We propose that inappropriate activation of microglia early in life impairs normal synaptic maturation and pruning during hippocampus development. These synaptic abnormalities persist into adulthood leading to long-term cognitive and behavioral deficits in adult BDS mice.

Disclosures: J. Delpech: None. **L. Wei:** None. **J. Hao:** None. **R.K. Lacher:** None. **A. Kaffman:** None.

Poster

809. Neuroinflammation: General

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant NS038079

Sanofi R & D

UCSF/BASIC pilot funds

Title: P75NTR mediates inflammatory responses by modulating differentiation of myeloid cells after TBI in mice

Authors: *S. LEE[1], N. SINGHAL[1], A. LIN[1], J. SACRAMENTO[1], B. CANOLLE[2], M.-N. CASTEL[2], S. DELBARY-GOSSART[3], B. FERZAZ[2], F. BONO[3], J. BRESNAHAN[1], M. BEATTIE[1];
[1]Neurolog. Surgery, Brain and Spinal Injury Ctr., UCSF, San Francisco, CA; [2]Sanofi R&D, Chilly-Mazarin, France; [3]Evotec, Toulouse, France

Abstract: Traumatic brain injury (TBI) leads to pro-inflammatory responses in both CNS and peripheral organs. The inflammatory responses may be involved in the subsequent development of clinical systemic inflammatory response syndrome, which eventually causes immune dysfunction and increases susceptibility to infection in chronic TBI patients (Keel and Trentz, 2005). Previously, we found that blocking the p75NTR signaling pathway by SARA, a selective p75NTR antagonist, preserves neuronal integrity and improves functional outcome after cortical contusion injury (CCI) TBI in rats. Strikingly, blocking p75NTR signaling reduces microglia activation as well as leukocyte trafficking into the injured brain (Lee et al., Neurotrauma 2014), suggesting p75NTR is involved in inflammatory responses after TBI. We used flow cytometry to examine the possible role of p75NTR in peripheral immune cell responses after TBI. *In vitro* studies using myeloid cells isolated from blood from WT mice demonstrated potent effects of LPS on differentiation of immature myeloid cells to mature myeloid cells and inflammatory macrophages ($CD11b^{+}F480^{+}Ly6C^{high}$). SARA treatment attenuated $CD11b^{+}F480^{+}Ly6C^{high}$ population, suggesting p75NTR is involved in differentiation of immature myeloid cells to inflammatory macrophages. SARA treatment also inhibited LPS-mediated increases in $Ly6C^{+}$ signal in splenocytes isolated from wild-type mice as well as reversed LPS-induced down-regulation of TCR, suggesting blocking p75NTR has beneficial effects on not only attenuation of inflammatory responses, but also preserve T cell function. Finally, we examined whether p75NTR mediates myeloid differentiation after TBI. Using a CCI-TBI model in C57Bl/6 WT mice, flow cytometric analysis showed that the population of mature macrophages ($CD11b^{+}F480^{+}$) and dendritic cells ($CD11b^{+}CD11c^{+}$) was significantly increased in the circulation as well as in the injured brain at 7 days after TBI. Interestingly, mice treated with

daily SARA (1 mg/kg i.p.) demonstrated reduced number of mature myeloid cells in both the circulation and the injured brain as well as reduced expression of pro-inflammatory markers in the spleen. Together, our new findings suggest that p75NTR mediates pro-inflammatory responses by modulating myeloid differentiation in the circulation., SARA, by blocking p75NTR, restores splenocyte T cell function and reduces myeloid differentiation. Such peripheral immuno-modulatory effect of SARA may contribute to its beneficial effects after cortical contusion.

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Poster

809. Neuroinflammation: General

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: CDMRP Grant W81XWH-09-2-0098

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Title: Chronic corticosterone primes the brain response to select neuroinflammatory agents by overexpression of Toll-like receptor 2 and S100A8: a potential role for microglia

Authors: *L. T. MICHALOVICZ, A. R. LOCKER, K. A. KELLY, D. B. MILLER, J. P. O'CALLAGHAN;
CDC-NIOSH, Morgantown, WV

Abstract: Neuroinflammation is commonly associated with chemically-induced neurotoxicity. We recently demonstrated that chronic exposure to the classic anti-inflammatory glucocorticoid, corticosterone (CORT), can markedly exacerbate, or “prime”, the neuroinflammatory response to select compounds (e.g., neurotoxicants or inflammogens). The mechanism by which this exacerbation is achieved is not yet understood. Here, we have exposed adult male C57BL/6J mice to several known neurotoxicants/AChE inhibitors/inflammogens that cause differential inflammatory responses following CORT pretreatment: methamphetamine (METH), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), diisopropyl phosphorofluoridate (DFP), chlorpyrifos

(CPO), pyridostigmine bromide (PB), lipopolysaccharide (LPS), and polyinosinic:polycytidylic acid (PIC). While a single exposure to these agents increases the expression of inflammatory cytokines in the brain (with the exception of PB), chronic (4-7 days) exposure to CORT (200 mg/L) in the drinking water prior to treatment enhanced the METH, DFP, CPO, and LPS induced neuroinflammation. The extension of this CORT effect across these multiple models, including those that cause neuronal damage and those that do not, suggests that the glial rather than neuronal response to the compounds is important for the proinflammatory effects of CORT. Toll-like receptors (TLRs) have been strongly implicated in glial priming of the neuroinflammatory response. Thus, we investigated whether TLR expression was altered in the brain in parallel with enhanced neuroinflammation. TLR2 was positively associated with the CORT neuroinflammatory priming effect exhibiting significant overexpression in METH, DFP, CPO, and LPS treated mice, but was unchanged, or even downregulated, in MPTP, PB, and PIC treated animals. In contrast, TLR4 expression was largely unaltered by chronic CORT pretreatment. The S100 calcium-binding protein A8 (S100A8), which has been positively associated with neuroinflammation, showed a similar profile to TLR2 expression across the multiple models, as expression was increased with CORT pretreatment in the brains of METH, DFP, CPO, and LPS exposed animals. While TLR2 expression has been characterized in microglial and astroglial priming, S100A8 overexpression is found in activated microglia, suggesting that microglia may be a primary cell type involved in CORT priming. Our data identify TLR2 and S100A8 as potential biomarkers of CORT priming of the brain inflammatory response, making them potential targets for treating diseases associated with microglial priming, such as Gulf War Illness.

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Poster

809. Neuroinflammation: General

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: CIHR

Title: Culturing adult mouse microglia

Authors: *A. D. GREENHALGH[1], B. W. MCCOLL[2], S. DAVID[3];
[1]McGill Univ., Montreal, QC, Canada; [2]The Roslin Inst. and Royal (Dick), Univ. of Edinburgh,

Edinburgh, United Kingdom; [3]Ctr. for Res. in Neurosci., Res. Inst. of the McGill Univ. Hlth. Ctr., Montreal, QC, Canada

Abstract: Microglia, the resident macrophages in the central nervous system (CNS) play a variety of roles during development, normal tissue homeostasis, defence against pathogen and response to injury and disease. Dissociated cultures of CNS cells has led to a greater understanding of all CNS cell types. A major caveat of such cultures is that cells are often isolated from perinatal animals. However, recent transcriptome data shows neonatal microglia have a significantly different profile to those isolated from the adult mouse, and that transforming growth factor beta (TGF-β) and Macrophage colony-stimulating factor (M-CSF) are needed for cultured adult microglia to retain their *in vivo* profiles. Here, we describe a simple protocol to extract and culture adult microglia with high purity using antibody-coated magnetic beads. We cultured isolated microglia from 12 week old mice in DMEM-F12 media containing FBS (10%) with combinations of recombinant M-CSF, conditioned media from L-929 cells (rich in M-CSF) or TGF- β, for 7 days. We find that L-929 conditioned media plus TGF- β provides the highest yield of microglia after 7 days in culture. Microglia under these conditions show a highly ramified morphology compared to those cultured in L929 media or M-CSF alone, and retain a similar transcriptional profile to freshly isolated microglia. These studies characterise an accessible protocol for the culturing adult microglia that allow the study of these cells in a variety of scenarios, including diseases of the adult CNS.

Disclosures: A.D. Greenhalgh: None. **B.W. McColl:** None. **S. David:** None.

Poster

809. Neuroinflammation: General

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NRF-2013R1A1A2062093

Title: Tonicity-responsive enhancer binding protein (TonEBP) regulates microglia activation and neuroinflammation

Authors: *D. KIM, H. KIM, B. LEE;
Univ. Ulsan, Ulsan, Korea, Republic of

Abstract: Activation of microglia, the resident macrophages of the central nervous system (CNS), is the hallmark of neuroinflammation in neurodegenerative diseases and other pathological conditions associated with CNS infection. Activation of microglia is often associated with neuronal death. Tonicity-responsive enhancer binding protein (TonEBP) is well known in the kidney as a transcription factor of Rel family such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB). Not limited in the kidney, TonEBP is expressed in various tissues, including brain, heart and thymus. Particularly in the brain, TonEBP is predominantly expressed in neurons. However, no clear evidence has yet been available for detailed function of TonEBP in neuroinflammation. Our studies focused on a possible role of TonEBP in mediating CNS inflammation. For *in vitro* studies, mouse microglial BV2 cells were treated with 100 ng/ml lipopolysacchride (LPS). For *in vivo* studies, mouse hippocampal tissues were isolated from C57BL/6 TonEBP wild and TonEBP heterozygote mice intracerebroventricularly administered with LPS (2.5 μg). Expression of TonEBP, pro-inflammatory cytokines, cyclooxygenase-2 (Cox2) and inducible nitric oxide synthase (iNOS) was evaluated using western blotting, quantitative real time PCR and enzyme-linked immunosorbent assay (ELISA). LPS stimulation increased TonEBP expression in microglial BV2 cells and mouse hippocampus in a time- and dose-dependent manner. Knockdown of TonEBP resulted in a decreased level of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), monocyte chemoattractant protein-1 (MCP-1) and interleukin-6 (IL-6), along with a significant decrease in iNOS and Cox2 expression and nitric oxide (NO) production. These results demonstrate role of TonEBP in mediating neuroinflammation in the microglia in response to LPS.

Disclosures: **D. Kim:** None. **H. Kim:** None. **B. Lee:** None.

Poster

809. Neuroinflammation: General

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIAAA Grant AA11605

Title: Distinct neuroimmune responses to different TLR agonists in brain slice cultures

Authors: *J. Y. ZOU, F. T. CREWS;
Univ. North Carolina, Chapel Hill, Chapel Hill, NC

Abstract: The Toll-like receptors (TLRs), a family of pattern recognition receptors and the hallmark of the host innate immunity, are increasingly implemented in various aspects of the central nervous system such as neuronal development, neural plasticity, neurogenesis and brain injury as well as in alcoholism. The present study used an *ex vivo* model of organotypic hippocampal-entorhinal cortex (HEC) slice cultures to investigate neuroimmune responses to several TLR agonists including Pam3CSK4 (TLR2), Poly:IC (TLR3), LPS (TLR4), Imiquimod (TLR7) and ODN D-SL03 (TLR9). HEC slices, prepared from P7 neonates and maintained in cultures for 11days prior to any treatment, were treated with Pam3CSK4 (100ng/ml), Poly:IC (10ug/ml), LPS (100ng/ml), Imiquimod (1ug/ml) and ODN D-SL03 (10ug/ml), all concentrations determined by a concentration-dependent study, for 2, 8, 24, 48 and 72hrs. RT-PCR analysis indicates that cytokine TNFα and IL-1β mRNA levels were rapidly increased following treatments of TLR agonists, reaching peak at 8hrs (10-100 fold increase depending on agonists), and drastically reduced (more than 80% decrease) but remained sustained high level from 24 to 72hrs. Even with only one episode of treatment (24hrs) and then HEC slices were maintained in agonist-free medium for 72hrs, cytokine genes were persistently increased by 3-10 folds depending on agonists. Signaling molecules including MyD88 and NF-kB were activated at early time point (peak at 2hrs but remained high at 8hrs). NRLP3 inflammasome pathway appears to be involved in neuroimmune responses induced by TLR3, TLR7 and TLR9. Activation of TLRs triggered rapid release of nuclear protein HMGB1 into culture media, with 6-12 fold increase in response to stimulation of TLR4, 7 and 9 at 8hr time point. HMGB1 is able to form complexes with all TLR agonists and HMGB1-TLR agonist complexes significantly potentiated neuroimmune gene induction. Microglia play key role in early neuroimmune responses to TLR activation since blockade of microglia activation by minocycline (10ug/ml) abolished TLR agonist-induced cytokine gene expression. Activation of TLR 2, 3 4 and 7 up-regulates neuron-released fractalkine but downregulates microglia-expressed receptor CX3CR1 genes. In contrast, activation of TLR 2, 4, 7 and 9 downregulates neuron-released CD200 but up-regulates microglia-expressed CD200 receptor genes. Together, these results may facilitate our understanding of the process and progression of neuroimmune responses to activation of different TLRs in brain. (supported by NIAAA)

Disclosures: J.Y. Zou: None. **F.T. Crews:** None.

Poster

809. Neuroinflammation: General

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Title: Cobalt protoporphyrin up-regulates cyclooxygenase-2 expression through a heme oxygenase independent mechanism

Authors: *H.-Y. LIN, D.-Y. LU;
China Med. Univ., Taichung City, Taiwan

Abstract: Cobalt protoporphyrin (CoPP) is a potent HO-1 inducer and generally known to be cytoprotective in various cell types. However, the roles of CoPP in regulating inflammation are intricate. Little is known about the CoPP induced cyclooxygenase-2 (COX-2) expression and its downstream signaling in microglial cells. In current study, CoPP caused concentration- and time-dependent increases in COX-2 expression in microglial cells. Furthermore, CoPP resulted in the dissociation of Apoptosis signal-regulating kinase (ASK) 1 from 14-3-3 and which contributed to ASK1 activation. Transfecting cells with ASK1 siRNA reduced CoPP-induced COX-2 expression. YO-PRO-1 probe accumulation results indicated that CoPP induced P2X7 receptors activation in microglia. Treatment of cells with P2X7 inhibitors effectively reduced CoPP-induced COX-2 expression. Moreover, CoPP also increased ERK, JNK and p38 phosphorylation. The current study also found that CoPP induced protein inhibitor of activated STAT 1 (PIAS1) degradation in concentration- and time- dependent manners. Furthermore, CoPP also caused PI3- kinase, Akt and Glycogen synthase kinase 3α/β (GSK3α/β) phosphorylation. Administration with PI3-kinase/Akt inhibitors reversed CoPP-mediated COX-2 expression and PIAS1 degradation. PIAS1 is reported to be involved in modulating anti-inflammatory response through negative regulation of transcription factors. On the other hand, treatment with GSK3α/β inhibitors enhanced CoPP-mediated COX-2 expression and PIAS1 degradation. These results suggest that CoPP induces COX-2 expression through activating P2X7 receptors and ASK1/MAP kinases pathways. CoPP also induced PIAS1 degradation via PI3-kinase/Akt and GSK3α/β pathways to modulate COX-2 expression in microglial cells. Our study provides a new insight into the regulatory effect of CoPP on neuroinflammation.

Disclosures: H. Lin: None. **D. Lu:** None.

Poster

809. Neuroinflammation: General

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 809.12/W25

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: Faculty of graduate studies mahidol university

Title: The effects of cadmium chloride on cell viability and inflammation in human astrocytes

Authors: *S. PHUAGKHAOPONG, D. OSPONDPANT, T. KASEMSUK, P. SATHAVORASMITH, P. VIVITHANAPORN;
Deparment of Pharmacol., Mahidol Univ., Bangkok, Thailand

Abstract: Cadmium is toxic to neurons and accumulates in the central nervous system. The exposure of cadmium is associated with neurodegenerative diseases such as Alzheimer's disease and Parkinson disease. However, the effects of cadmium on astrocytes remain unclear. Previous studies reported that prolonged exposure to cadmium induces inflammation in variety of tissues, including kidneys, liver and lungs, by increasing the expression of cyclooxygenase-2 (COX-2), interleukin 6 (IL-6), and interleukin 8 (IL-8). Herein we hypothesize that cadmium may cause neurodegenerative diseases by inducing cytotoxicity and inflammation of astrocytes. Thus, this study aims to investigate the effects of cadmium on the viability of astrocytes and the expression of COX-2 and cytokines/chemokines in U-87 MG and A172 human astrocytoma cells. Cells were treated with 0.1-100 μM of cadmium chloride for 6, 24 and 48 hours. Twenty-four hours after exposure to cadmium chloride, the median toxic concentration (TC50) measured by MTT assays are about 22.85 and 16.18 μM in U-87 MG and A172 astrocytes, respectively. Cell viability was decreased in a time- and concentration-dependent manner, compared to the mock-treated group. At 6-hour exposure, the non-toxic dose of cadmium chloride at 10 μM promoted the expression of COX-2, IL-6 and IL-8 assessed by real time PCR assays. In summary, the present results indicate that cadmium is toxic to human astrocytes and induces the production of inflammatory mediators i.e. prostaglandins, cytokines/chemokines. These direct toxic effects to astrocytes together with the up-regulation of inflammation may play a role in central nervous system dysfunction and contribute to the pathophysiology of neurodegenerative diseases.

Disclosures: S. Phuagkhaopong: None. **D. Ospondpant:** None. **T. Kasemsuk:** None. **P. Sathavorasmith:** None. **P. Vivithanaporn:** None.

Poster

809. Neuroinflammation: General

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 809.13/W26

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: Cyberonics, Inc.

Alexander von Humboldt Foundation

U01 NS05158

Title: Status epilepticus induces lasting inflammatory changes in the hippocampus

Authors: *N. H. VARVEL[1], M. JUCKER[2,3], R. DINGLEDINE[1];
[1]Pharmacol., Emory Univ., Atlanta, GA; [2]Hertie Inst. for Clin. Brain Res., Tuebingen, Germany;
[3]DZNE-German Ctr. for Neurodegenerative Dis., Tuebingen, Germany

Abstract: The prolonged seizures of generalized status epilepticus (SE) trigger a series of molecular and cellular events that produce cognitive deficits and can eventually culminate in the appearance of spontaneous seizures, i.e. epilepsy. Initial known events include transient opening of the blood brain barrier (BBB) and reactive astrocytosis accompanied by activation of microglia, the resident brain macrophage. Between one and three days after SE circulating monocytes infiltrate the brain in a Ccr2-dependent manner. Inhibiting recruitment of these cells reduces the induction of IL-1β message by 50%. The goals of the present study were to utilize immunohistological approaches to examine the nature of blood brain barrier opening after SE and the innate and adaptive immune responses after systemic injection of the chemoconvulsant, kainic acid (KA). While peripheral Ccr2+ monocytes infiltrate the brain after SE, few CD3+ T-cells were encountered in the brain parenchyma. Only a few macrophages in each section were positive for hemosiderin by Prussian blue staining suggesting cerebral hemorrhage was not common after KA-induced SE. Fibrinogen staining was elevated in the KA-treated mice when compared to saline-treated controls. However, fibrinogen was confined to the vasculature and only rarely was observed in the parenchyma. On average 43,000 Iba1+ cells were counted in the control hippocampus. One day after SE, the number of Iba1+ cells in the hippocampus increased 2-fold and was further elevated 4-fold over controls at the three and 14 day time points. The Iba1+ and CX3CR1+ cells remained clustered around the sites of hippocampal damage up to 14 days after SE. Numerous markers of innate immune cell activation including CD11b, CD45, CD68 and CD169 were elevated in the hippocampus of KA-treated mice one and three after SE when compared to control hippocampi. Notably, these same indices of innate immune cell activation remained elevated when compared to saline-treated controls 14 days after SE. Taken together, these data argue against a generalized opening of the BBB immediately after SE and suggest that monocyte-dominated infiltration into the brain is regulated in part by Ccr2 signaling axis. Furthermore, our histological findings indicate that the neuroinflammatory response is mediated in part by central and peripheral innate immune cells of myeloid lineage with little evidence for an adaptive immune response at the time points examined.

Disclosures: **N.H. Varvel:** None. **M. Jucker:** None. **R. Dingledine:** None.

Poster

809. Neuroinflammation: General

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 809.14/W27

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: Texas Garvey Foundation

PO1 HL088052

R56HL062579

Title: Chronic intermittent hypoxia associated oxidative stress and inflammation in male rats

Authors: *B. SNYDER[1], B. SHELL[2], J. CUNNINGHAM[2], R. L. CUNNINGHAM[2];
[1]Univ. of North Texas Hlth. Sci. Ctr., Ft Worth, TX; [2]UNT Hlth. Sci. Ctr., Ft. Worth, TX

Abstract: Sleep apnea is a common comorbidity in neurodegenerative diseases such as Parkinson 's disease and Alzheimer's disease. Increased inflammation and oxidative stress (OS) are hallmarks of both sleep apnea and neurodegeneration. The elevated OS associated with sleep apnea may be a mechanism leading to altered inflammatory profiles within specific brain nuclei. To examine the role of OS on inflammation in the brain, we used an animal model of chronic intermittent hypoxia (CIH) which mimics the hypoxemia experienced by sleep apnea patients. Adult male rats were exposed to 8 hours of 6 minute cycles of alternating room air oxygen and 8% oxygen levels during the light cycle for seven days. Plasma was assessed for OS and inflammatory markers. Also, inflammatory markers and OS were measured in five different brain nuclei: the substantia nigra (SN), hippocampus (H), entorhinal cortex (ETC), rostral ventrolateral medulla (RVLM), and the solitary tract nucleus (NTS). Our results showed that CIH is associated with increased circulating OS and inflammation. However, widely varying effects of OS and inflammation within different brain regions were observed in response to CIH. CIH had a significant protective effect in the hypothalamus, known for regulating homeostasis. A pro-inflammatory profile in the SN and ETC was observed as well as a significant increase in KC-GRO, a cytokine associated with recruitment of neutrophils and angiogenesis. This indicates that OS induced by mild hypoxemia is capable of having both protective and damaging effects on the brain. In regions associated with homeostasis, a protective effect of CIH was found. However, in brain regions associated with neurodegeneration, a damaging effect of CIH was observed, indicating that hypoxemia may be a contributor of neurodegenerative diseases.

Disclosures: **B. Snyder:** None. **B. Shell:** None. **J. Cunningham:** None. **R.L. Cunningham:** None.

Poster

809. Neuroinflammation: General

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 809.15/W28

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: DOD Grant W81XWH-11-1-0637

Title: The danger-associated molecular pattern HMGB1 mediates the neuroinflammatory effects of methamphetamine

Authors: *M. G. FRANK[1], S. ADHIKARY[3], J. L. SOBESKY[2], M. D. WEBER[2], L. R. WATKINS[2], S. F. MAIER[2];
[2]Psychology and Neuoscience, [1]Univ. of Colorado, Boulder, CO; [3]NIDA, NIH, Washington, D.C., DC

Abstract: Methamphetamine (METH) induces neuroinflammatory effects, which may contribute to the neurotoxicity of METH. However, the mechanism by which METH induces neuroinflammation has yet to be clarified. A considerable body of evidence suggests that METH induces cellular damage and distress, particularly in dopaminergic neurons. Damaged neurons release danger-associated molecular patterns (DAMPs) such as high mobility group box-1 (HMGB1), which induces pro-inflammatory effects in microglia by signaling through toll-like receptor 4 (TLR4) or the receptor for advanced glycation endproducts (RAGE). Indeed, HMGB1 released from damaged neurons has been found to mediate neuroinflammation in models of seizure, ischemia, and traumatic brain injury. Therefore, we explored the notion here that METH induces neuroinflammation indirectly through the release of HMGB1 from damaged neurons, which then signals through TLR4 on microglia to induce a pro-inflammatory cytokine response. Adult male Sprague-Dawley rats were injected IP with METH (10 mg/kg) or vehicle (0.9% saline). Neuroinflammatory effects of METH were measured in nucleus accumbens (NAcc), ventral tegmental area (VTA) and prefrontal cortex (PFC) at 2h, 4h and 6h after injection. To assess whether METH directly induces pro-inflammatory effects in microglia, whole brain or striatal microglia were isolated using a Percoll density gradient and exposed to METH (0, 0.1, 1, 10, 100, or 1000 uM) for 24h and pro-inflammatory cytokines measured. To determine the role of HMGB1 in the neuroinflammatory effects of METH, animals were injected intra-cisterna magna with the HMGB1 antagonist box A (10 ug) or vehicle (sterile water). 24h post-injection,

animals were injected IP with METH (10 mg/kg) or vehicle (0.9% saline) and 4h later neuroinflammatory effects measured in NAcc, VTA, and PFC. METH induced robust pro-inflammatory effects in NAcc, VTA, and PFC as a function of time and pro-inflammatory analyte measured. In particular, METH induced profound effects on interleukin-1 beta (IL-1) in NAcc (2h) and PFC (2h and 4h). Exposure of microglia to METH *in vitro* failed to induce a pro-inflammatory response, but rather induced significant cell death as well as decreases in cytokines at the high concentrations of METH. Pre-treatment with the HMGB1 antagonist box A blocked the neuroinflammatory effects (IL-1) of METH in NAcc, VTA and PFC. The present results suggest that HMGB1 mediates, in part, the neuroinflammatory effects of METH and thus may alert CNS innate immune cells to the toxic effects of METH.

Disclosures: M.G. Frank: None. **S. Adhikary:** None. **J.L. Sobesky:** None. **M.D. Weber:** None. **L.R. Watkins:** None. **S.F. Maier:** None.

Poster

809. Neuroinflammation: General

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 809.16/W29

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: Seed Funding for Basic Science Research 201311159171 to RC

Title: The effect of sevoflurane in systemic inflammation-induced cognitive dysfunction

Authors: *W. LEUNG[1], O. T. W. NG[2], S. S. Y. CHENG[2], C. H. L. HUNG[2], J. M. T. CHU[1], R. C. C. CHANG[2], G. T. C. WONG[1];
[1]Dept. of Anaesthesiology, [2]Dept. of Anat., The Univ. of Hong Kong, Hong Kong, Hong Kong

Abstract: With longer lifespan and medical advancement, about half of the population over 65 may have undergone operative procedures with anaesthesia and subsequently be more prone to post-operative cognitive dysfunction (POCD). Upon surgical procedures, systemic inflammation is elicited and the production of peripheral cytokines would prime the microglia after direct entry across the blood-brain-barrier. Subsequent neuroinflammation could affect cognitive functions leading to POCD. Risk factors of POCD are not limited to age, but also the modulatory effects of anaesthetic agents. The effect of a commonly used inhalational anaesthetic agent, sevoflurane remains unclear. To demonstrate the modulatory effect of sevoflurane on systemic inflammation-induced cognitive dysfunction, 3-month-old of young and 18-month-old of aged mice were subjected to sevoflurane exposure and administration of lipopolysaccharides. After treatment, the

results from the Morris water maze showed an increase in the latency to find the hidden platform in both young and aged mice, implying its effect on spatial memory. Modulations in the expression level of presynaptic, postsynaptic and synaptic vesicle membrane proteins within different brain regions were detected in Western Blot. Differential changes in both endocytosis and exocytosis of synaptic vesicles were detected by measuring the uptake and release of FM1-43, a lipophilic styryl fluorescent dye in synaptosome fraction of brain tissues. These results indicate that sevoflurane exerts its effect on systemic inflammation-induced cognitive dysfunction.

Disclosures: **W. Leung:** None. **O.T.W. Ng:** None. **S.S.Y. Cheng:** None. **C.H.L. Hung:** None. **J.M.T. Chu:** None. **R.C.C. Chang:** None. **G.T.C. Wong:** None.

Poster

809. Neuroinflammation: General

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 809.17/W30

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Title: The effect of immunosuppressive and immunomodulatory drugs in a cellular model of brain inflammation: involvement of nitric oxide-mediated neuronal death

Authors: C. NEVEU, E. ANDRIAMBELOSON, *S. WAGNER;
NEUROFIT, ILLKIRCH, France

Abstract: Neuroinflammation is now recognized as a critical process in different neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, stroke and multiple sclerosis. Microglia and astrocytes are key players in neuroinflammation since they release a wide variety of proinflammatory mediators, including nitric oxide (NO). In the present study, the potential neuroprotective effect of immunosuppressive (dexamethasone) and immunomodulatory (doramapimod) drugs was investigated in lipopolysaccharide (LPS) -stimulated microglia/astrocyte/neuron co-cultures, with special attention to the involvement of NO in the death of neurons. Stimulation of co-cultures with LPS produced substantial, sustained production of NO in the medium. Significant death of dopaminergic neurons was observed 5 days post-stimulation. Neuronal death was fully prevented by dexamethasone treatment but not by doramapimod although both drugs fully suppressed the production of NO. It is noteworthy that the antioxidant resveratrol markedly reduced NO production along with partial inhibition of neuronal death. These data indicates that inflammation-mediated neuronal death in

microglia/astrocyte/neuron co-cultures involves both NO-dependent and NO-independent pathways.

Disclosures: **C. Neveu:** None. **E. Andriambeloson:** None. **S. Wagner:** None.

Poster

809. Neuroinflammation: General

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 809.18/W31

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: Ministerio de Economia y Competividad, Gobierno de España

International Foundation for Research in Paraplegia

Title: Administration of IL-4 regulates macrophage polarization and reduces secondary tissue damage after spinal cord injury

Authors: ***I. FRANCOS-QUIJORNA**, A. MARTÍNEZ-MURIANA, R. LÓPEZ-VALES; Univ. Autonoma De Barcelona, Bellaterra, Spain

Abstract: Spinal cord injury (SCI) elicits an inflammatory response that comprises mainly microglia and peripheral blood macrophages. Several studies indicate that these cells contribute to tissue damage and functional deficits in several central nervous system disorders, including SCI. However, they have also shown to promote repair in other experimental paradigms. These paradoxically conflicting actions of microglia and macrophages may depend on the signals in the lesion milieu and the phenotype that they can adopt, “classical” M1 activation (pro-inflammatory and cytotoxic effects) or “alternative” M2 activation (anti-inflammatory and tissue repair effects). After SCI, microglial cells and macrophages display predominantly M1 phenotype, however, the factors that impede M2 polarization in SCI are not fully known. Answers to these questions are of high relevance for advancing therapeutics to treat SCI. In the present work we show that the expression of IL-4, one of the main M2 polarizing factor, is not induced in the contused spinal cord. To assess whether the lack of IL-4 accounts for the deficit in M2 polarization after SCI, we administrated mouse recombinant IL-4 into the contused spinal cord. We found that acute administration of IL-4 after SCI led to minor induction of M2 markers only in microglia. However, when IL-4 was given at 48 hours post-injury, the expression of Arg1 and CD206 was strongly induced in both, microglia and macrophages, adopting a hybrid M1/M2 phenotype that remained stable for at least four days. Interestingly, at 4 days post-injection (6

days post-injury), besides myeloid cells, we found an immune cell population (CD45high, CD11blow) that was only present in IL-4-treated animals. Further analysis on this immune cell subtype revealed that they were phenotypically compatible with resolution-phase macrophages, suggesting that IL-4 drives microglia and macrophage polarization towards a mixed M1/M2 as well as to a resolution-phase phenotype. We finally found that IL-4 led to beneficial effects in functional and histopathological outcomes after SCI, despite IL-4 was injected 2 days after lesion. Overall, our data indicates that the lack of IL-4 in the contused spinal cord impedes the shift in the polarization of microglia and macrophages in SCI, which leads to functional deficits and secondary tissue damage. We show that a single administration of IL-4 at 2 days after SCI is effective in reducing functional impairments and tissue damage. Our data suggest that treatment with IL-4 could be a new approach with a wide therapeutic window for the treatment of acute SCI, for which there are no effective treatment yet.

Disclosures: I. Francos-Quijorna: None. **A. Martínez-Muriana:** None. **R. López-Vales:** None.

Poster

809. Neuroinflammation: General

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 809.19/W32

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: Japan Science and Technology Agency, CREST

Grants-in-Aid from Ministry of Education, Culture, Sports, Science and Technology, Japan

Title: The critical role of proteolytic relay through cathepsins B and E in the phenotypic change of microglia/macrophage

Authors: *N. JUNJUN[1], Z. WU[1], Y. HAYASHI[1], C. PETERS[2], K. YAMAMOTO[3], H. QING[4], H. NAKANISHI[1];
[1]Dept. of Aging Sci. and Pharmacol., Kyushu Univ., Fukuoka, Japan; [2]Albert Ludwigs Universitt Freibrug, Freiburg, Germany; [3]Proteolysis Res. Laboratory, Kyushu Univ., Fukuoka, Japan; [4]Beijing institute of technology, Beijing, China

Abstract: In spite of its clinical importance, little is known about the mechanisms underlying the phenotypic shift of microglia/macrophages. We herein show the critical role of a proteolytic

relay through cathepsins B (CatB) and E (CatE) as a phenotypic switch in microglia/macrophages. Hypoxic/ischemia (HI) caused extensive brain injury in neonatal wild-type mice, but not in CatB-/- mice. Furthermore, HI induced M1-like followed by M2-like polarization of microglia/macrophages in wild-type mice, but only M2-like polarization in CatB-/- mice. A specific CatB inhibitor CA-074Me prevented the activation of nuclear factor-κB (NF-κB) by inhibiting autophagic IκBα degradation following an HI-like injury. Rather surprisingly, CatE has been shown to increase the CatB expression after HI by the liberation of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) from microglia through the proteasomal pathway. Thus, a proteolytic relay through the early CatE/TRAIL-dependent and late CatB-dependent pathways may play an essential role in the M1-like phenotypic polarization of microglia/macrophages.

Disclosures: **N. Junjun:** None. **Z. Wu:** None. **Y. Hayashi:** None. **C. Peters:** None. **K. Yamamoto:** None. **H. Qing:** None. **H. Nakanishi:** None.

Poster

809. Neuroinflammation: General

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 809.20/W33

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: SFI/IA/1537

Title: Lentiviral overexpression of interleukin-1β in the hippocampus induces neurogenesis-associated cognitive deficits in adult male rats

Authors: ***C. M. HUESTON**, C. S. Ó'LÉIME, D. A. KOZAREVA, J. F. CRYAN, Y. M. NOLAN;
Univ. Col. Cork, Cork, Ireland

Abstract: Adult neurogenesis within the subgranular zone of the hippocampus, which is integral for normal cognitive function, can be affected by inflammatory tone. Previous studies have demonstrated that elevated levels of the pro-inflammatory cytokine interleukin-1β (IL-1β) in the hippocampus, has detrimental effects on some aspects of memory and cognitive function, as well as a negative impact on the proliferation and survival of newly born neurons. Thus, the current study aimed to assess whether long-term increased expression of IL-1β through lentiviral mediated overexpression of the protein would alter performance in a series of hippocampal-dependent tasks including pattern separation, which has previously been demonstrated to be

dependent on hippocampal neurogenesis. A lentivirus overexpressing IL-1β (3.7x10^3 TU) or mCherry as a control was bilaterally injected into the dorsal hippocampus of adult male Sprague-Dawley rats (n = 10). Three weeks after injection a battery of behavioural tests were carried out, including spontaneous alternation in the Y-maze (a measure of working memory), the location recognition task (a measure of spatial memory), pattern separation in a modified location recognition task, and the open field test. Hippocampal tissue was collected 4 days following behavioural testing for analysis by real-time RT-PCR for changes in gene expression levels of IL-1β and neurogenesis-related markers. Increased mRNA expression of IL-1β was confirmed in the hippocampus following lentiviral IL-1β overexpression. IL-1β overexpression did not alter spontaneous alternations in the Y-maze test, or location discrimination in the location recognition task. In the pattern separation task, rats overexpressing IL-1β in the dorsal hippocampus were not able to pattern separate in the small separation condition, but were able to do so with a large separation, suggesting hippocampal neurogenesis-associated dysfunction. No change in locomotor activity was observed in the open field test. Analysis of the gene expression levels of neurogenic markers Ki67 and DCX, as well as expression of the nuclear receptor TLX, a neurogenesis regulator which has previously been shown to be reduced in response to IL-1β treatment *in vitro*, are currently underway. The current results indicate that long-term hippocampal exposure to the pro-inflammatory cytokine IL-1β has detrimental effects on the neurogenesis-associated pattern separation cognitive task. Thus, the ability to pattern separate may be more susceptible to the detrimental effects of chronic inflammation than other hippocampal-dependant functions such as working memory and location recognition memory.

Disclosures: C.M. Hueston: None. **C.S. Ó'Léime:** None. **D.A. Kozareva:** None. **J.F. Cryan:** None. **Y.M. Nolan:** None.

Poster

809. Neuroinflammation: General

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 809.21/W34

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: Russian ministry of education and science (# 413)

Title: Intracellular acidification during the acute phase of neuroinflammation

Authors: *A. A. TYRTYSHNAIA[1], A. M. KLESCHEVNIKOV[2], M. KHOTIMCHENKO[1]; [1]Far Eastern Federal Univ., Vladivostok, Russian Federation; [2]Neurosciences, Univ. of California San Diego, La Jolla, CA

Abstract: Maintenance of the brain pH level within the physiological norm is an important component of the central nervous system homeostasis. pH levels strongly impact 3D-structure of proteins and other biological molecules, thus affecting functional activity of enzymes, receptors, and ion channels. In some conditions, the capacity of pH-regulatory system can be overcome by various pathological factors resulting in alterations of the brain acidity. pH changes are found in nervous tissue pathologies associated with neuroinflammation, such as Alzheimer's disease. We hypothesized that acute neuroinflammation may result in substantial shifts of the intracellular pH (pHi) levels, and that such pHi changes may contribute significantly to cognitive abnormalities in neurodegenerative disorders. To test this hypothesis, we developed an *in vitro* model of acute neuroinflammation. Measurements of intracellular pH levels were performed on transverse hippocampal slices using ratiometric pH-sensitive fluorescent dye BCECF. Hippocampal slices of 3 month old mice were incubated for 1 h in ACSF containing either LPS (1 μg/ml) or vehicle. After washing-out, the slices were stained with BCECF-AM (1 μM, 30 min at 32°C) and transferred to the recording chamber for measurements of pHi in pyramidal neurons of the CA1 region. We observed that pHi levels were not different in the LPS vs. Veh treated slices at 2-3.5 h after the treatment. However, at a later period (3.5-7 h) pHi levels were in Veh: 7.28 ± 0.05; in LPS: 6.92 ± 0.07, $p < 0.001$, showing a difference of about 0.36 pH units. To test if the LPS treatment induced neuroinflammation, densities of IL1β-positive neurons have been measured in the LPS and Veh-treated slices using immunohistochemistry. The density was in Veh: 312.66 ± 50.45; in LPS: 598.72 ± 77.44 cells/mm2, $p < 0.001$, confirming induction of neuroinflammation by '*in vitro*' treatment with LPS. To examine whether or not the effects of neuroinflammation on pHi levels could be observed *in vivo*, LPS or Veh were injected in 12 month old mice, and the levels of pHi were measured 8 h later. Again, pHi level was significantly reduced in slices from LPS vs. Veh -injected animals (Veh: 7.13 ± 0.03; LPS: 6.78 ± 0.08, $p = 0.001$). Thus, our results show that acute neuroinflammation causes a profound temporal intracellular acidification in the CA1 pyramidal neurons, which may affect neuronal and synaptic functions in pathologies.

Disclosures: **A.A. Tyrtyshnaia:** None. **A.M. Kleschevnikov:** None. **M. Khotimchenko:** None.

Poster

809. Neuroinflammation: General

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 809.22/W35

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Title: Microglia activation and monocyte recruitment in LPS induced neuroinflammation in mouse brain

Authors: *Q. CHEN[1], V. B. CHEUNG[2], C. HAN[2], S. MIYAKE[1], K. TAJINDA[1], H. ITO[1]; [1]Neuroscience, Astellas Res. Inst. of Ameri, Skokie, IL; [2]Master of Biotech. program, Northwestern Univ., Evanston, IL

Abstract: Neuroinflammation is not only a common characteristic in neurodegenerative diseases, but also associated with mental health conditions such as depression, bipolar disease, Schizophrenia and posttraumatic stress disease (PTSD), etc. Microglial cells are the resident immune cells in CNS which operate as critical effector and regulator of neuroinflammatory processes in the brain. The prolonged microglia activation has produced pro-inflammatory cytokines and other inflammatory mediators which disrupt the neuro-immune homeostasis in brain. In addition, in neuro-psychiatric diseases and neurological diseases, the immune-to-brain communication has been altered in pathological conditions such as inflammation and stress. The increased monocyte trafficking into the brain has further elevated pro-inflammatory cytokine levels and affected the innate immune function in brain which induces a wide range of detrimental effects in neuronal function. Therefore, targeting on the microglia activation and monocyte trafficking into brain will provide a novel approach for the treatment of neuro-immunological pathophysiology-involved neuropsychiatric and neurological diseases. In present studies, we established *in vitro* primary cultured microglia, primary microglia/ neuron co-culture systems. We investigated microglia M1 and M2 polarization by using LPS- and IL4-stimulated *in vitro* model and evaluated pro-inflammatory chemo-cytokine expression alteration by using qRT-PCR and multiplex ELISA assays. In the meantime, we studied the microglia activation and monocyte recruitment in endotoxin LPS-challenged neuroinflammation mice model. Acute and sub-chronic LPS systemic injection could induce the robust neuroinflammation phenotype in the brain. We also established microglia isolation protocol and developed flow cytometry assays to quantify microglia activation and monocyte trafficking in adult mouse brain. We demonstrated a significant increase in $CD11b^{+}CD45^{high}$ monocytes in the LPS-challenged brain samples. Furthermore, we are working to develop the flow cytometry assays to measure microglia activation marker in inflamed brain samples. These studies will help us to understand the microglia / immune cell mechanism in neuroinflammation and facilitate anti-inflammatory targets validation in neuropsychiatric diseases treatment.

Disclosures: Q. Chen: A. Employment/Salary (full or part-time):; Q, Chenis a full-time employee in Astellas Research Institute of America, a subsidy of Astellas Pharma. **V.B. Cheung:** A. Employment/Salary (full or part-time):; V. Cheung works as internship in Astellas Research Institute of America. **C. Han:** A. Employment/Salary (full or part-time):; C. Han works as a internship in Astellas Research Institute of America. **S. Miyake:** A. Employment/Salary (full or part-time):; S. Miyake is a full-time employee in Astellas Research institute of America, a subsidy of Astellas Pharma. **K. Tajinda:** A. Employment/Salary (full or part-time):; K. Tajinda is a full-time employee in Astellas Research Institute of America, a subsidy of Astellas Pharma. **H. Ito:** A. Employment/Salary (full or part-time):; H. Ito is a full-time employee in Astellas Research Institute of America, a subsidy of Astellas Pharma..

Poster

809. Neuroinflammation: General

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 809.23/W36

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Title: Characterization of the translocator protein (TSPO) ligand [^{3}H]PBR28 binding in BV2 microglial cell line homogenates and in rodent brain and spinal cord autoradiography

Authors: H. XIAO[1], *J. LI[2,1], M. MORIN[1], L. J. MARTIN[1], M. P. JOHNSON[1];
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Abstract: **BACKGROUND:** It has been well documented that the up-regulation of the translocator protein (18 kD) (TSPO) in microglia and astrocytes in response to lesions and/or neuroinflammation is directly associated with the degree of damage. Increased TSPO ligand binding has been investigated as a molecular *in vivo* sensor of neuronal damage and inflammation in patients with neurodegenerative diseases that are characterized by neuronal loss in discrete areas of the CNS. In addition, TSPO ligands show neuroprotective and anti-inflammatory effects in experimental models of peripheral neuropathies and traumatic brain injury. These ligands might therefore also be valuable for the treatment of neurologic diseases with inflammation-related pathophysiology. Here, we report TSPO expression in a cultured murine BV-2 microglial cell line and studied the effects of the TSPO ligand [^{3}H]PBR28 on microglial functions. We also use frozen section autoradiography to study TSPO radioligand [^{3}H]PBR28 binding in experimental neuroinflammatory models. **METHOD**: TSPO ligand [^{3}H]PBR28 saturation and competition binding assays were performed in murine BV-2 microglial homogenates. Autoradiography of [^{3}H]PBR28 binding for the activated microglial/astrocytes was assessed in sections of spinal cord from an animal model of experimental allergic encephalomyelitis (EAE) and after intrastraital Lipopolysaccharide (LPS)-induced neuroinflammation. **RESULTS**: TSPO was highly expressed in BV2 microglial cells line. High affinity binding of [^{3}H]PBR28 was detected in membranes prepared from BV-2 cells (Bmax = 7156 fmol/mg; Kd = 0.332 nM). Multiple known TSPO ligands potently displaced [^{3}H]PBR28 from BV2 homogenates. Autoradiograph of LPS-induced rat striatum lesions showed high intensity [^{3}H]PBR28 binding in the LPS-challenged hemisphere vs. saline injected hemisphere of rat brain. In an EAE model, autoradiography displayed a higher binding to grey matter with [^{3}H]PBR28 in EAE mouse spinal cord than in sham controls. **CONCLUSION**: [^{3}H]PBR28 has high binding affinity in murine BV-2 microglial cell membrane.

Autoradiography result suggested that TSPO was upregulated in glia with the EAE model and were also strongly induced after intrastriatal LPS-challenge in the rat.

Disclosures: **H. Xiao:** A. Employment/Salary (full or part-time):; Eli Lilly and Company. **J. Li:** A. Employment/Salary (full or part-time):; Eli Lilly and Company. **M. Morin:** A. Employment/Salary (full or part-time):; Eli Lilly and Company. **L.J. Martin:** A. Employment/Salary (full or part-time):; Eli Lilly and Company. **M.P. Johnson:** A. Employment/Salary (full or part-time):; Eli Lilly and Company.

Poster

809. Neuroinflammation: General

Location: Hall A

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Program#/Poster#: 809.24/W37

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NINDS Grant NS079387-01

NINDS Grant P30NS069346

Medical Research Foundation of Oregon

Title: The Protein Phosphatase 4 complex is required for proper axotomy-induced glial immune responses

Authors: ***L. WINFREE**, M. A. LOGAN;
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Abstract: Neuronal damage induced by injury, stroke or neurodegenerative disease all elicit a swift immune response from glial cells, including upregulation of glial immune genes, directed migration to injury sites and glial clearance of damaged neurons through phagocytic engulfment. Collectively, these glial responses are critical for minimizing damage to the CNS. For example, proper glial clearance of degenerating neurons before they become necrotic attenuates broader inflammatory responses. Thus, it is essential that we understand the cellular and molecular mechanisms behind these important protective glial responses to assist efforts to therapeutically target glial cells in acute and chronic CNS conditions. To identify new molecular players that contribute to glial phagocytic function after injury, we are using a well-established acute axotomy assay in the powerful genetic model system *Drosophila melanogaster*. Through *in vivo* RNAi screening strategies, we have discovered that the evolutionarily conserved Protein Phosphatase 4 (PP4) serine/threonine phosphatase complex is required for proper glial clearance

of degenerating axons. The trimeric PP4 complex consists of one catalytic subunit (PP4c) and two regulatory subunits (PP4r2 and Falafel). We find that glial-specific knockdown of any of these subunits in the adult brain leads to delayed glial clearance of axonal debris after olfactory nerve axotomy. In addition, inhibition of the PP4 complex in adult glia leads to reduced recruitment of glial membranes to injury sites after axotomy, suggesting that defects in glial membrane dynamics may contribute to reduced phagocytic function in PP4-knockdown glia. Previous work has suggested that the PP4 complex regulates activation of the RhoGTPase Rac1 and is also required for proper cell migration *in vitro* (Martin-Granados, 2008). Importantly, Rac1 is essential for proper glial membrane recruitment and phagocytic clearance of degenerating axons in the adult *Drosophila* brain (Lu, 2014). Thus, we are now investigating the possibility that phosphatase activity of the PP4 complex directs Rac1-mediated glial migratory behavior in the context of innate glial immune responses to neurodegeneration. Collectively, this work highlights the importance of conserved serine/threonine phosphatase-dependent pathways as critical candidate effectors of glial immunity and also reveals a new family of molecules that could be targeted to harness the neuroprotective power of glial cells in the context of injury and neurodegenerative disease.

Disclosures: L. Winfree: None. **M.A. Logan:** None.

Poster

809. Neuroinflammation: General

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: LVB is supported by a postdoc fellowship from INMiND (HEALTH-F2-2011-278850)

Title: Functional expression of the intermediate-conductance Ca^{2+}-activated K^+ channel, $K_{Ca}3.1$, in microglia isolated from human neocortical tissue

Authors: L. V. BLOMSTER[1,2], D. STRØBÆK[1], C. HOUGAARD[1], L. PINBORG[2], J. D. MIKKELSEN[2], *P. CHRISTOPHERSEN[1];
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Abstract: Microglia are key players in neuroinflammatory processes and are considered to be cellular targets for development of drugs against neurological diseases. The $K_{Ca}3.1$ channel (*KCNN4*) has been suggested to participate in both pro-inflammatory and restorative

mechanisms of microglia cells. However, most studies are hitherto carried out using cell lines or primary rodent microglia cultures, while little is known about the presence and role of $K_{Ca}3.1$ in human microglia. Here we employ electrophysiological whole-cell measurements combined with selective pharmacological tools to study the functional expression of $K_{Ca}3.1$ in cultured human microglia. Cells were isolated from healthy brain neocortical tissue removed as part of neurosurgical treatment of epilepsy. Based on immunocytochemistry, the cultures contained 92% microglia, 1% astrocytes but no neurons or oligodendrocytes. The microglia were resting and responded to a lipopolysaccharide (LPS) challenge by the release of TNFα. A major fraction (84 %) of the cultured and unstimulated human microglia cells expresses functional $K_{Ca}3.1$ channels as demonstrated by a significant increase in the voltage-independent current at -40 mV upon application of NS309, a potent $K_{Ca}3.1/K_{Ca}2$ channel activator, followed by a significant decrease in response to NS6180, a highly selective $K_{Ca}3.1$ inhibitor (n=75). The "$K_{Ca}3.1$ window" thus defined as the delta current between full activation and full inhibition was estimated to be 239 ± 46 pA. Activation and inhibition of the $K_{Ca}3.1$ channel had a significant impact on the microglia cell membrane potential as measured by current clamp experiments. The resting membrane potential was -24 ± 17 mV and application of NS309 induced a hyperpolarization of the membrane potential to -67 ± 13 mV. Subsequent co-application of NS6180 reversed this effect and restored the resting membrane potential ($p<0.001$, n=7). To activate the microglia the cell cultures were incubated with interleukin-4 (IL-4) or LPS for 2-4 days. IL-4 treated human microglia had a larger cell membrane area, as determined by whole cell capacitance (32 pF), compared to both unstimulated (20 pF, $p<0.001$) and LPS treated (24 pF, $p<0.05$) microglia ($n\geq18$). The fraction of microglia expressing functional $K_{Ca}3.1$ channels was unchanged after treatment with IL-4 or LPS. Microglia stimulated with IL-4 had only a small increase in the overall $K_{Ca}3.1$ current ($p<0.05$, n=28) which is quantitatively in contrast to previous findings in rat microglia. Taken together the data shows that $K_{Ca}3.1$ is functionally expressed on resting human microglia as well as on cells continuously challenged with standard pro- and anti-inflammatory stimuli.

Disclosures: **L.V. Blomster:** A. Employment/Salary (full or part-time):; Linda V. Blomster. **D. Strøbæk:** A. Employment/Salary (full or part-time):; Dorte Strøbæk. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dorte Strøbæk. **C. Hougaard:** A. Employment/Salary (full or part-time):; Charlotte Hougaard. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Charlotte Hougaard. **L. Pinborg:** None. **J.D. Mikkelsen:** None. **P. Christophersen:** A. Employment/Salary (full or part-time):; Palle Christophersen. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Palle Christophersen.

Poster

809. Neuroinflammation: General

Location: Hall A

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Program#/Poster#: 809.26/W39

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Title: Modulation of Interleukin-10 immunosuppression by Tofacitinib (CP 690,550) in the mouse microglial cell line BV-2

Authors: *K. C. BRADLEY, J. RIVARD, A. JAMES, J. DAVID, L. BRANDENBURG, N. LEE, R. FUERSTENBERG, K. BRUMBAUGH, L. LEONG, G. WEGNER, K. REAGAN; R&D Systems, Inc., Minneapolis, MN

Abstract: The anti-inflammatory cytokine interleukin-10 (IL-10) is known to be necessary for down regulating pro-inflammatory responses toward pathogens. IL-10 inhibits the production of many cytokines downstream of its receptor via the JAK1/Tyk2-STAT3 signaling pathway. The small molecule Tofacitinib, CP 690,550, is a selective inhibitor of JAK family cytoplasmic tyrosine kinases. It has been shown to potently inhibit both JAK3- and JAK1-dependent STAT activation. Mouse microglial BV-2 cells are an established *in vitro* model for neuronal inflammation and have been reported to respond to IL-10 immunosuppression in a manner similar to primary mouse microglial cells. In this model, IL-10 pretreatment attenuates IL-6 and TNF-α secretion in BV-2 cells treated with interferon-γ (IFN-γ) and lipopolysaccharide (LPS) cells. In order to better understand the potential effects of inhibiting the immunosuppressive effects of IL-10, we examined the effects of Tofacitinib on the secretion of pro-inflammatory cytokines and activation of the JAK/STAT signaling pathway. The Mouse XL Cytokine Array was used to screen cell culture supernates from mouse microglial BV-2 cells with or without treatment with IFN-γ and LPS for six hours. We identified increased secretion of several cytokines upon IFN-γ/LPS treatment, including CCL3/4, CCL5, CCL12, CD40, CXCL2, CXCL9, CXCL10, G-CSF, ICAM-1, IL-1α, IL-1ra, IL-6, IL-27, SerpinE1, and TNF-α. The secretion of these cytokines were found to decrease by IL-10 treatment prior to IFN-γ/LPS treatment. We observed that Tofacitinib treatment attenuated the immunosuppressive action of IL-10 by restoring the secretion of CCL2, CCL5, G-CSF, CCL3/4, and CXCL2 to levels near IFN-γ/LPS treatment alone. Interestingly, NEDD8 E1 activating enzyme inhibitor MLN4924 inhibition of the Nuclear Factor-κB (NFκB) signaling pathway did not appear to abrogate IL-10 immunosuppression. Array results were confirmed by using a quantitative Luminex multiplex assay. Because Tofacitinib is known to inhibit JAK family kinases, we evaluated the tyrosine phosphorylation of their substrate STAT proteins. Western blot analysis revealed that Tofacitinib inhibited phosphorylation of Tyr701-STAT1 and Tyr705-STAT3 in a time-dependent manner in BV-2 cells treated with IL-10 and IFN-γ/LPS. While it is well established that LPS-induced

transcription of pro-inflammatory cytokines is regulated by mitogen-activated protein kinases and NFκB, the molecular mechanisms involved in IL-10 suppression of pro-inflammatory cytokine expression are largely unknown and may be affected indirectly by the action of Tofacitinib.

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Poster

809. Neuroinflammation: General

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NS88206

ES10586

Title: Pesticide-induced mitochondrial dysfunction activates nlrp3 inflammasome signaling pathway in primary murine microglia

Authors: S. SARKAR[1], N. PANICKER[1], M. NEAL[1], H. JIN[1], A. CHARLI[1], *V. ANANTHARAM[2], A. KANTHASAMY[1], A. KANTHASAMY[1];
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Abstract: The NLRP3 inflammasome signaling pathway has recently been recognized as a major player in neuroinflammatory insults in the CNS. Oxidative stress and mitochondrial dysfunction are also known to play a key role in pathophysiological processes of many neurodegenerative diseases, including Parkinson's disease (PD). To date, the relationship between mitochondrial defects and neuroinflammation is not well understood. In the present study, we show that neurotoxic pesticide-induced mitochondrial impairment amplifies the NLRP3 inflammasome proinflammatory cascade in primary microglia. Treatment of primary mouse microglia with LPS induced NLRP3 and pro-IL1β expression. Interestingly, exposure of LPS-primed microglial cells to the mitochondrial complex-1 inhibitory pesticides, rotenone and tebufenpyrad, activates the NLRP3 inflammasome and processing of pro-ILβ to IL-1β in a time and dose-dependent manner, indicating that mitochondrial impairment heightened the pro-

inflammatory response in microglia. Morphological analysis revealed that rotenone and tebufenpyrad significantly increased mitochondrial circularity and solidity in LPS-primed microglia as well as decreased mitochondrial perimeter relative to unprimed microglia, indicating the augmentation of mitochondrial fission during neurotoxic pesticide-induced inflammasome activation. Immunocytochemistry (ICC) revealed that rotenone and tebufenpyrad exposure induced mitochondrial superoxide production in LPS-primed microglia and ICC also showed co-localization of NLRP3 with mitochondrial superoxide in rotenone-treated LPS-primed microglia but not in rotenone-alone-treated microglia. Furthermore, following LPS-priming, more IL-1β was released during exposure tebufenpyrad than to rotenone, indicating that tebufenpyrad is a more potent activator of inflammasome signaling. Collectively, our studies demonstrate for the first time that mitochondrial impairment resulting from neurotoxic pesticide exposure can activate NLRP3 inflammasome signaling in microglia, further augmenting proinflammatory events in the brain. Our findings have important implications in the pathogenesis and progression of environmentally-linked PD.

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Poster

809. Neuroinflammation: General

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: CIHR Frederick Banting and Charles Best Canada Graduate Scholarship

Title: Sensory ganglia of injured adult mice have augmented populations of Iba1-immunopositive macrophages in the absence of functional p75 neurotrophin receptor

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Abstract: Peripheral nerve injury and disease trigger the activation and infiltration of immune cells (e.g., macrophages) in the affected nerve and associated sensory ganglia. These peripheral macrophages release various cytokines which can heighten the immune response and exacerbate injury (e.g., neuropathic pain) and disease progression (e.g., osteoarthritis). Neurotrophins such as nerve growth factor (NGF) are known mediators of inflammation and monocytic cell

infiltration. The neurotrophin receptor, p75 neurotrophin receptor (p75NTR) binds to all members of the neurotrophin family as well as cytokines with similar low affinity. Both neurotrophins and cytokines have been implicated in the pathophysiological features of sensory neuron dysfunction. The aim of this study was to determine whether the expression of p75NTR in adult mice affects the activation of macrophages in sensory ganglia after unilateral partial sciatic nerve ligation or unilateral injection of monosodium-iodoacetate (MIA) into the hind limb footpad. While wild-type (p75+/+) and p75NTR knockout (p75-/-) mice both displayed a significant increase in the density of Iba1-immunopositive macrophages in the ipsilateral lumbar dorsal root ganglia (DRG) at 1 and 2 weeks post-nerve ligation, only p75-/- mice exhibited a significant increase in the density in the contralateral DRG at 1 week post-injury as well. As for MIA-induced inflammation, p75+/+ and p75-/- mice both displayed increases in the densities of macrophages in the ipsilateral and contralateral DRG at 1 week post-injection; p75-/- mice (as compared to p75+/+ mice) exhibited a significant increase density in the ipsilateral DRG at 2 weeks after MIA injection. Effects seen in p75NTR-deficient mice are curious because macrophages in the mouse DRG (damaged or otherwise) do not express this receptor. Since sciatic nerve ligation and hind limb footpad inflammation both stimulate increased receptor levels by ganglionic glial cells (i.e., satellite and Schwann cells), we propose that p75NTR on these glial cells plays a role in restricting the activation and infiltration of macrophages in the sensory ganglia of adult mice. One possible mechanism may be through p75NTR-mediated sequestration of increased levels of neurotrophins and/or cytokines by glial cells, thereby minimizing macrophage activation and/or infiltration in the murine DRG following injury and inflammation.

Disclosures: **L.J. Smithson:** None. **M.D. Kawaja:** None.

Poster

809. Neuroinflammation: General

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: MR/J006572/1

Title: Primary microglia isolated from neonatal mice provide a model for the study of NLRP3 inflammasome and the effect of long-term hypoxia

Authors: *R. A. WICKENS[1], L. VER DONCK[2], S. J. BAILEY[1], A. B. MACKENZIE[1]; [1]Univ. of Bath, Bath, United Kingdom; [2]Dept. of Neuroscience, Janssen Res. & Develop., Janssen Pharmaceutica, Beerse, Belgium

Abstract: Microglia act as the primary immune cells of the brain and have inflammatory properties aimed at clearing infected or damaged tissue. Neuroinflammation is thought to play a key role in the pathology of many diseases, including Alzheimer's disease, Parkinson's disease and even psychiatric disorders such as depression (Amor, S. et al. 2010. Immunol. 129(2); 154-169). The NLRP3 inflammasome is a multi-protein complex responsible for caspase-1 activation and the production of inflammatory cytokines IL-1β and IL-18. Furthermore, while most *in vitro* studies use 20% O2, the O2 availability within the brain is thought to range between 0.5-7% O2 (Ivanovic, Z. 2009. J Cell Physiol. 219(2); 271-275). We have previously reported that NLRP3 inflammasome signalling is sensitive to acute hypoxia (4 hr; 5% O2) in a microglia cell line (Wickens, R. et al. 2013. pA2 Online. 11(3) 058P). Here, we have aimed to establish a primary microglia culture using mild trypsinization to study NLRP3 inflammasome expression in long term cultures under different oxygen conditions. Mixed glial cultures were obtained from neonate (P0.5) C57BL/6 pups and cultured in normoxic tissue culture conditions for 3 weeks (~20% O2/5% CO2). Astrocytes were removed via mild trypsin incubation (0.0625% w/v). Microglia were kept in conditioned media for 24 hours prior to testing. To study protein expression, cells were treated with lipopolysaccharide (E. Coli LPS; 0.1 μg/ml; ≤4hr) before cell lysates were collected for western blot. To study inflammasome activity, cells were primed with LPS (0.1 μg/ml; ≤4hr) prior to treatment with ATP (5 mM; 30 minutes) to assess IL-1β release by ELISA. All cells were CD11b+/GFAP-, confirming the presence of microglia. We observed a time-dependant increase in NLRP3 (4 hr, $p=0.06$) and proIL-1β (4 hr, $p<0.05$) expression following LPS stimulation, along with the expression of adaptor protein ASC and P2X7 in stimulated and unstimulated microglia. We then observed an LPS-dependant IL-1β release following cell stimulation with ATP (4 hr LPS, $p<0.001$). Furthermore, caspase-1 inhibition (Ac-YVAD-cmk; 10 μM) caused a significant reduction in ATP-induced IL-1β release ($p<0.05$), indicating the process is caspase-1-dependant. Together, these data suggest the presence of a functional NLRP3 inflammasome. These findings confirm the expression and activity of the NLRP3 inflammasome in neonatal primary microglia. The 3-week microglia culture provides a platform to study NLRP3 inflammasome signalling and the effect of chronic hypoxia, which will give a more accurate insight into microglia activation and inflammasome signalling within the brain and during neuroinflammatory disease.

Disclosures: **R.A. Wickens:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutica. **L. Ver Donck:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutica. **S.J. Bailey:** None. **A.B. Mackenzie:** None.

Poster

809. Neuroinflammation: General

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: University of Minnesota College of Veterinary Medicine

Title: Central nervous system injury - newly observed abscopal effect of hind-limb radiation

Authors: *C. FEIOCK[1], M. YAGI[2], A. MAIDMAN[3], *A. RENDAHL[3], S. K. HUI[2], D. M. SEELIG[1];
[1]Vet. Clin. Sci., Univ. of Minnesota, Saint Paul, MN; [2]Therapeut. Radiology, Univ. of Minnesota, Minneapolis, MN; [3]Dept. of Statistics, Univ. of Minnesota, Saint Paul, MN

Abstract: Chemotherapy-related cognitive impairment (CRCI), otherwise known as "chemobrain" or "chemo fog," is a well-known phenomenon in cancer survivors, with approximately 30% of breast cancer survivors experiencing impairment up to 10+ years after treatment. The most prominent and enduring declines occur in learning and memory, attention, executive function, and processing speed, leading to severe disturbances in quality of life. However, these same deficits have also been described in cancer survivors who received radiation therapy only, or radiation in combination with chemotherapy (multimodal treatment), yet the consequences of non-brain directed radiotherapy (NBRT) have been poorly characterized and remain largely unstudied. While there have been several studies examining the mechanisms underlying the impact of chemotherapy on the development of CRCI, including the increased production of cytokines and reactive oxygen species, the biological consequences, and therefore mechanisms, of brain injury due to NBRT are unknown. In order to describe the functional and cellular effects of NBRT on the brain, adult female BALB/c mice were given a single-dose of 18-Gy orthovoltage ionizing radiation to the right hind limb. To assess the impact of NBRT on brain glucose metabolism, a subgroup of NBRT mice (n=3) were evaluated by FDG-PET 3 days post irradiation. To assess the longitudinal effects of NBRT, mice were sacrificed at 3-, 14-, and 30-days post irradiation and brains were examined by immunohistochemistry (IHC) for activated astrocytes (GFAP) and microglia (Iba1). The findings in NBRT mice were compared with: (i) mice treated with methotrexate (MTX), a chemotherapeutic agent associated with CRCI and (ii) untreated controls. As compared to untreated controls, FDG-PET imaging revealed decreased FDG uptake in all brain areas of NBRT mice and IHC showed a marked regional and global increase in the number of GFAP and Iba1 positive cells, indicating reactive astrocytosis and microgliosis, respectively, at all 3 sacrifice days. This increase in both GFAP and Iba1 positive cells was equal to the response seen following treatment with MTX alone, potentially indicating

a shared mechanism of CNS damage following either treatment, and also pointing to a potential for a compounding effect if both treatments are given together, as is seen in multimodal cancer treatment. Our initial findings indicate brain bystander effects associated with NBRT and support a role for its potential involvement in CRCI.

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Poster

809. Neuroinflammation: General

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Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Title: Role of N-acylethanolamine acid amidase (NAAA) in (neuro)inflammation

Authors: *S. PONTIS, A. RIBEIRO, F. PALESE, N. REALINI, A. ARMIROTTI, D. PIOMELLI;
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Abstract: Fatty acid ethanolamides (FAEs) such as palmitoylethanolamide (PEA) and oleoylethanolamide (OEA) are lipid-derived mediators that potently inhibit inflammation and exert neuroprotective effects; their levels change during central nervous system (CNS) pathological conditions affecting the progression of the neuroinflammatory process. PEA and OEA are preferentially degraded by the intracellular cysteine amidase, N-acylethanolamine acid amidase (NAAA). We have previously demonstrated that NAAA inhibition normalizes PEA and OEA levels, which are severely reduced in several inflammatory models. Moreover our preliminary studies in mouse models of neuroinflammation suggest that NAAA mRNA and protein levels increase in activated microglia. To further characterize the role of NAAA in inflammatory diseases we generated conditional transgenic mice overexpressing NAAA (NAAA ki) in CD11b-positive cells. NAAA ki were obtained by crossing NAAA conditional knock-in heterozygous mice carrying a NAAA isoform-1 coding sequence within the Rosa26 locus with CD11b-Cre transgenic mice. NAAA ki mice display increased levels of NAAA mRNA and protein in the CNS and peripheral organs as demonstrated by qPCR and western blot analysis. Immunofluorescence analysis of lung sections shows increased levels of NAAA in macrophages from NAAA ki mice compared to WT littermates. Moreover, alveolar macrophages of NAAA ki mice display clear signs of activation: they are hypertrophic and show enlarged cytoplasm, nuclear decentralization and increased levels of iNOS. Analysis of CNS sections indicates that

NAAA expression is increased in Iba1-positive cells. In NAAA ki mice it is possible to identify two morphologically distinct types of Iba1-positive cells: (1) activated microglia expressing high levels of NAAA, which show large and ameboid shape; and (2) non-activated microglia with characteristic ramified form, expressing lower levels of NAAA. When challenged with intranasal LPS NAAA ki mice display higher inflammatory parameters - increased leukocyte migration into the lungs, TNF-alpha, IL-6 and MCP-1, compared to wt littermates - confirming that NAAA overexpression increases susceptibility to inflammatory stimuli. Preliminary studies on mouse models of Parkinson's disease (PD) (intrastriatal 6-OHDA injection) suggest that NAAA ki mice are also more sensitive to neuroinflammatory stimuli than wt littermates. NAAA ki mice may provide a valuable tool to elucidate the role of NAAA in PD and other neuroinflammatory conditions.

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Poster

810. Neuroinflammation: Cellular mechanisms

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Program#/Poster#: 810.01/W45

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIHR

Wellcome Trust

MRC

Title: Kinetic analysis of the translocator protein positron emission tomography ligand [18F]GE-180 in the healthy human brain

Authors: *C. L. FEENEY[1], G. SCOTT[1], J. RAFFEL[1], C. COELLO[2], A. GOLDSTONE[1], G. SEARLE[2], R. GUNN[1,2], D. SHARP[1];
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Abstract: Background The translocator protein (TSPO) is upregulated in activated microglia in response to inflammatory stimuli, making TSPO a good a biomarker for neuroinflammation (1). Positron emission tomography (PET) is used to image neuroinflammation by targeting TSPO. First generation radioligands, for example, [11C]PK11195, have been criticised for poor signal-

to-noise ratio and high nonspecific binding which can limit accurate quantification (2) [18F]GE-180 is a new TSPO radiotracer that demonstrates superiority to [11C]PK11195 in animal studies (3), and has the advantage of a longer half-life negating the need for an on-site cyclotron. Aim Our main objective was to evaluate the ability of [18F]GE-180 to quantify TSPO in brains of healthy human participants and to establish the best kinetic modelling approach. Our secondary objective was to determine whether there was any difference in binding between the high and mixed affinity binders (HABS and MABS), determined by a TSPO polymorphism that has been shown to affect binding of other TSPO tracers (4). Methods Ten participants (5 HAB, 5 MAB), 28-57 years old, underwent 90-min PET scans with arterial sampling after bolus injection of [18F]GE-180. One- and two-tissue compartmental models and Logan graphical methods were performed, enabling estimation of the volume of distribution (VT) in regions of interest (ROIs) in the brain. Results A two-tissue compartment model described the data well. The delivery rate constant (K1) was in the region of 0.1 mL/min across all brain regions. Average estimated VT values ranged from 0.3-0.6 ml/cm3. There was no significant difference in VT between HAB and MAB across all ROIs examined. Conclusion A two-tissue compartment model is an appropriate way to model the GE-180 PET signal. We found no clear evidence for a genetic effect of the TSPO polymorphism on binding. Investigation of [18F]GE-180 in clinical populations will be helpful in assessing fully the utility of the tracer for the investigation of activated microglia *in vivo*. References 1.Chen, M. K. et al. Translocator protein 18 kDa (TSPO): molecular sensor of brain injury and repair. Pharmacology & therapeutics 118, 1-17 (2008). 2.Kropholler, M. A. et al. Evaluation of reference tissue models for the analysis of [11C](R)-PK11195 studies. JCBFM 26, 1431-1441, (2006). 3.Dickens, A. M. et al. Detection of microglial activation in an acute model of neuroinflammation using PET and radiotracers 11C-(R)-PK11195 and 18F-GE-180. JNM 55, 466-472, (2014). 4.Owen, D. R. et al. An 18-kDa translocator protein (TSPO) polymorphism explains differences in binding affinity of the PET radioligand PBR28. JCBFM 32, 1-5, (2012).

Disclosures: C.L. Feeney: None. **G. Scott:** None. **J. Raffel:** None. **C. Coello:** None. **A. Goldstone:** None. **G. Searle:** None. **R. Gunn:** None. **D. Sharp:** None.

Poster

810. Neuroinflammation: Cellular mechanisms

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 810.02/W46

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant NS081014

NIH West Virginia Stroke CoBRE (P20 GM109098)

West Virginia University Startup Funds

Title: Brain endothelial cell tissue nonspecific alkaline phosphatase directs immunometabolic responses at the blood-brain barrier

Authors: *C. M. BROWN[1], S. JUN[2], W. WANG[1], C. THORE[3];
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Abstract: Brain microvascular endothelial cells (BMECs) form a network of cerebral microvessels that comprise the blood-brain barrier (BBB). The BBB preserves cerebral homeostasis, in part, by coordinating central and peripheral systemic inflammatory responses. Thus, preservation of the cerebral microvasculature is essential in acute and chronic neurological dysfunction. Histological staining of tissue nonspecific alkaline phosphatase (TNAP) activity is a well-characterized marker of cerebral microvessels, yet a physiological role for TNAP in BMECs and the BBB is unclear. The goal of this study was to determine a functional role for TNAP in BMECs that supports the preservation of cerebral homeostasis. We tested the hypothesis that acute systemic inflammation impairs TNAP activity in BMECs, leading to disrupted cellular metabolism in these cells, and, ultimately, impaired cerebral homeostasis. To test this hypothesis *in vivo*, female mice (8-12 weeks) were subjected to a moderate experimental sepsis model of acute systemic inflammation for 48h. Cerebral microvessels were stained for TNAP activity, followed by unbiased stereology to quantify the total length of TNAP-positive (TNAP+) microvessels in frontal cortex and striatum. Our results showed that experimental sepsis significantly reduced the number of TNAP+ cerebral microvessels in frontal cortex and striatum compared to their sham-injured counterparts. We then employed a human brain endothelial cell model of the BBB, hCMEC/D3 (D3) cells, to test our hypothesis *in vitro*. Treatment of D3 cells with a novel TNAP inhibitor suppressed TNAP activity. Similarly, lipopolysaccharide (LPS), tumor necrosis factor-α (TNFα), or interferon-γ (IFNγ) challenge to D3 cells also decreased extracellular and secreted TNAP activity. Since TNAP is known to regulate ATP metabolism in osteoblasts and chondrocytes, we tested whether inhibition of TNAP activity alters mitochondrial function in D3 cells. Assessment of BMEC bioenergetics with the Seahorse XF96 analyzer revealed that inhibition of TNAP activity suppressed oxygen consumption, maximal respiration, and glycolytic reserve in the presence of LPS, TNFα, or IFNγ. These results suggest a novel immunometabolic mechanism that supports a putative anti-inflammatory role for TNAP at the BBB. More importantly, these results also suggest the utility of exogenous TNAP administration as a therapeutic strategy to limit neurological dysfunction in acute and chronic systemic inflammation.

Disclosures: **C.M. Brown:** None. **S. Jun:** None. **W. Wang:** None. **C. Thore:** None.

Poster

810. Neuroinflammation: Cellular mechanisms

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Program#/Poster#: 810.03/W47

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: VR 2012-2992

Title: Pivotal role of choroid plexus in TLR2-induced leukocyte infiltration to central nervous system

Authors: *A. MOTTAHEDIN[1], J. EK[2], P. SVEDIN[2], A.-L. LEVERIN[2], P. L. SMITH[2], S. NAIR[2], H. HAGBERG[3,4], C. MALLARD[2];
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Abstract: The barriers of central nervous system (CNS) protect the brain from pathogens, potentially hazardous molecules and cells of the immune system. Dysregulation or breakage of the barriers may lead to harmful invasion of the CNS by pathogens and/or an activated immune system (e.g. during meningoencephalitis). The molecular mechanisms of physiological or pathological opening of the CNS barriers are yet to be elucidated. Here we show that peripheral administration of a synthetic bacterial lipoprotein and ligand for Toll-like receptor 2 (Pam3CSK4, PAM) induce massive infiltration of neutrophils and inflammatory monocytes to the cerebrospinal fluid (CSF) and brain of neonatal mice and rats as well as adult mice. In contrast, a TLR 4 ligand, LPS, did not cause leukocyte infiltration, although it elicited similar level of peripheral inflammation. Flow cytometry and immunohistochemistry studies revealed recruitment of inflammatory cells to choroid plexus following PAM administration suggesting it as one of the potential routes of leukocyte entry into the CSF and brain. RNA sequencing on choroid plexus of neonatal mice treated with PAM or LPS, revealed significant differences in expression level of hundreds of genes. Ingenuity Pathway Analysis (IPA) of data strongly predicted activation of integrin signalling (z-scores 3.12 and -0.2 for PAM and LPS respectively), Rho GTPase signalling (z-scores 3.0 and 0.18 for PAM and LPS respectively) and leukocyte extravasation signalling (z-scores 3.83 and 1.97 for PAM and LPS respectively) by PAM; the signalling pathways that may mediate adhesion, transmigration and extravasation of leukocytes through choroid plexus. Taken together, this study demonstrates a TLR2-mediated

leukocyte infiltration to the CNS through choroid plexus and suggests several potential underlying mechanisms that may facilitate the leukocyte trafficking.

Disclosures: **A. Mottahedin:** None. **J. Ek:** None. **P. Svedin:** None. **A. Leverin:** None. **P.L. Smith:** None. **S. Nair:** None. **H. Hagberg:** None. **C. Mallard:** None.

Poster

810. Neuroinflammation: Cellular mechanisms

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NEI grant 5R01EY019525-02

Title: Retinal microglia and Müller glia crosstalk during BMP7 mediated gliosis

Authors: ***S. DHARMARAJAN**[1], T. MCCRAY[1], N. SHEIBANI[2], T. L. BELECKY-ADAMS[1]; [1]INDIANA UNIVERSITY-PURDUE UNIVERSITY INDIANAPOLIS, Indianapolis, IN; [2]Ophthalmology and Visual Sci., UNIVERSIY OF WISCONSIN, MADISON, WI

Abstract: **PURPOSE**: Retinal microglia are key players of the innate immune system of the central nervous system. Upon injury and damage, they become "activated", undergoing characteristic molecular and morphological changes. The primary retinal glial cells, Müller glia, as well as the retinal astrocytes also undergo activation, a process called reactive gliosis, following retinal injury. During reactive gliosis, several factors have been previously shown to be regulated, including bone morphogenetic proteins. Our lab has previously shown that BMP7 is able to trigger Müller cell gliosis, however the mechanism is unclear. In this study we aim to determine if BMP7 is able to trigger activation of retinal microglia, and whether this activation could lead to upregulation of factors which could potentially enhance Müller cell gliosis. **METHODS**: Mouse retinal microglial cells *in vitro* as well as mature mice were exposed to vehicle, lipopolysaccharide (LPS; a known activator of microglia), or BMP7 to test and compare activation. RT-qPCR was performed on RNA from treated microglial cells and mouse retinal tissue for markers of activation. Immunohistochemistry of microglial cells, retinal tissue sections and retinal flatmount preparations were also performed to assess changes in morphological characteristics. Conditioned medium from BMP7 treated retinal microglia was used to treat retinal Müller glial cells and its RNA was assessed via RT-qPCR for changes in gliosis markers. **RESULTS**: Mouse retinal microglia following LPS treatment *in vitro* showed an upregulation in RNA levels of inflammatory markers previously shown to be indicative of activation.

Morphological analysis of microglia *in vitro* as well as in mouse eyes injected with LPS intravitreally, revealed an increase in total cellular area as well as an increase in number of branch points. BMP7 treatment showed an increase in RNA levels of GM-CSF and BMP7 in the microglia, while an increase in INF-γ was observed in Müller glia. Furthermore, an increase in the morphological characteristics was also observed following BMP7 treatment *in vitro* and *in vivo*. Treatment of retinal glia with conditioned medium from activated microglia led to upregulation of some of the markers associated with gliosis, indicative of a positive regulation on retinal gliosis. **CONCLUSION**: Initial findings are indicative of crosstalk between reactive retinal glia and activated microglia. BMP7 does trigger activation of retinal microglia, and both microglia and Müller glia upregulate factors potentially playing a role in regulation of activation states of the two glial cell types.

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Poster

810. Neuroinflammation: Cellular mechanisms

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NRF Grant 2013R1A1A2061607

Korean Health technology R&D Grant A111345

Ministry of Health & Welfare Grant HI14C3331

Title: Phenotypic screening to identify small-molecule inhibitor of glia-mediated neuroinflammation: Target identification and biological effects of a novel compound

Authors: *G. SONG[1], Y. NAM[2], M. JO[2], J. KOO[3], S. PARK[3], K. SUK[2];
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Abstract: Neuroinflammation is a key process for many neurodegenerative diseases. Therefore, targeting neuroinflammation by small molecules has been thought to be a potential therapeutic strategy. In this study, we have used microglia cell-based phenotypic screening system to identify a novel compound (N-carbamoylated urethane) as a potent anti-neuroinflammatory

agent. The compound inhibited LPS-induced pro-inflammatory cytokines, iNOS, and NO production showing anti-inflammatory effect in microglia. With a fluorescence-guided target identification method (FITGE), we have identified PPAR gamma as a target of the compound. PPRE reporter assay showed that the compound activated PPAR-gamma, but not PPAR-delta or alpha, confirming PPARgamma is a target protein of the compound. In fact, the anti-inflammatory effect of the compound was attenuated by PPAR-gamma knockdown or PPAR-gamma antagonist. In addition, the compound clearly increased the expression of PPAR-gamma-mediated anti-inflammatory genes such as arginase-1 in microglia as well as astrocytes. The anti-neuroinflammatory effect of the compound was also observed in LPS-injected mouse, demonstrating the therapeutic potential of the compound in neuroinflammatory diseases.

Disclosures: G. Song: None. **Y. Nam:** None. **M. Jo:** None. **J. Koo:** None. **S. Park:** None. **K. Suk:** None.

Poster

810. Neuroinflammation: Cellular mechanisms

Location: Hall A

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: Craig H. Neilsen Foundation

Wings for Life

Adelson Medical Foundation

Title: The immune receptors dectin-1 and TLR2 are required for conditioning lesion-induced axon protection following spinal cord injury

Authors: *C. YOON[1], K. S. CARBAJAL[2], K. T. BALDWIN[1], B. M. SEGAL[2], R. J. GIGER[1]; [2]Holtom-Garrett Program in Neuroimmunology and Multiple Sclerosis Center, Dept. of Neurol., [1]Univ. of Michigan Sch. of Med., Ann Arbor, MI

Abstract: Under certain circumstances, activation of innate immunity promotes robust regeneration of severed axons following injury to the rodent optic nerve or spinal cord. The underlying molecular mechanisms, however, remain incompletely understood. Our laboratory recently identified that activation of the pattern recognition receptors dectin-1 and toll-like receptor 2 (TLR2) on myeloid cells triggers an inflammatory cascade that enables injured retinal ganglion cells (RGC) to extend lengthy axons that grow far beyond the lesion site in the adult

mouse optic nerve. In the current study, we hypothesized that dectin-1 and TLR2 also participate in the conditioning lesion (CL)-induced effects toward dorsal root ganglion (DRG) neurons that form the dorsal columns in the spinal cord. Histochemical studies show a decrease in macrophage infiltration into DRGs seven days following CL in both dectin-1-/- and dectin-1-/-;TLR2-/- mutant mice, when compared to wild-type controls. Flow cytometric analysis confirmed that following CL, neutrophil, dendritic cell, and macrophage accumulation in DRGs is reduced. Importantly, CL-induced neurite outgrowth of primary DRG neurons is reduced in mutants compared to CL-induced neurite outgrowth of wild-type DRG neurons. Specifically, neurite outgrowth, as assessed by NF200 immunolabeling, is significantly decreased both in dectin-1-/- and dectin-1-/-;TLR2-/- null cultures. Most noticeably, 5-weeks following spinal cord injury, axonal "die-back" in the injured dorsal columns is much more prominent in CL-dectin-1-/-;TLR2-/- mice compared to CL-wildtype mice. This suggests that activation of a dectin-1/TLR2-dependent immune response is required to protect dorsal column axons from "die-back". The long-term goal of this research is to identify the signaling pathways that are activated by the innate immune system to enable CNS axon regeneration following injury or disease. (Supported by Craig H. Neilsen Foundation, Wings for Life, and Adelson Medical Foundation)

Disclosures: C. Yoon: None. **K.S. Carbajal:** None. **K.T. Baldwin:** None. **B.M. Segal:** None. **R.J. Giger:** None.

Poster

810. Neuroinflammation: Cellular mechanisms

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Program#/Poster#: 810.07/X3

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Title: Mitigating microglial-mediated neuroinflammation: the sur1-trpm4 channel regulates calcium-sensitive induction of inos

Authors: *D. B. KURLAND, J. A. STOKUM, V. GERZANICH, J. M. SIMARD; Neurosurg., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Microglia, the resident immune cells of the central nervous system, play a critical role in health and disease. Following injury, microglia upregulate inducible nitric oxide synthase (iNOS), and can exert neurotoxic effects by releasing large quantities of nitric oxide (NO). Expression of iNOS, and many other pro-inflammatory genes, is regulated in part by Ca2+ influx and Ca2+-dependent transcription factors, such as nuclear factor of activated T cells (NFAT). The expression of the non-selective cation channel Sur1-Trpm4 may be one molecular

mechanism by which microglia dynamically modulate Ca2+ influx. We hypothesized that microglial Sur1-Trpm4 plays a role in microglial-mediated neuroinflammation by regulating the calcium-sensitive induction of iNOS by controlling NFAT activity. To test this hypothesis, we evaluated microglial cells before and after stimulation by the Toll-like receptor 4 (TLR4) agonist lipopolysaccharide (LPS). Protein expression was evaluated by immunohistochemistry, western blot, and co-immunoprecipitation (Co-IP). Quantitative PCR (qPCR) was employed to evaluate gene expression. Functional Sur1-Trpm4 activity was evaluated electrophysiologically. Confocal microscopy and the calcium-sensitive fluorescent dye, Fluo-4, was used to dynamically measure intracellular calcium. Extracellular nitrite, a by-product of NO formation, was measured to evaluate iNOS activity. Glibenclamide and 9-Phenanthrol were employed to pharmacologically inhibit Sur1 and Trpm4, respectively. We found that microglia express functional Sur1-Trpm4 channels, whose activity modulated Ca2+ oscillations induced by TLR4 ligation. Inhibition of Ca2+, Sur1-Trpm4 or NFAT all significantly abrogated the induction of iNOS. The activation of NFAT induced by TLR4 ligation was modulated by inhibition of Sur1. Our results strongly support our hypothesis that Sur1-Trpm4 regulates the calcium-sensitive induction of iNOS by controlling NFAT activity. These observations have impactful therapeutic implications. Inhibition of Sur1-Trpm4 using the well-tolerated sulfonylurea glibenclamide (a.k.a. glyburide) may be a promising approach to limit the deleterious effects of microglial-mediated neuroinflammation.

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Poster

810. Neuroinflammation: Cellular mechanisms

Location: Hall A

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NSFC grant 81271172

Title: High-fat-diet induced obesity increases nociceptive responses and spinal glial activation

Authors: Y.-Q. GUO[1], J. LEI[1], M.-Q. LIU[1], *K.-Y. FU[2];
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Abstract: Altered nociceptive responses are frequently seen in obese individuals. However, animal experimental evidence is lacking and molecular mechanism is less known. Low grade chronic inflammation of obese individual may contribute to increased nociceptive activity. Microglia are the central immune and inflammatory cells and has been well implicated in the generation and maintenance of pain hypersensitivity. In this study, we aimed to investigate nociceptive behaviors, spinal glial activation and associated proinflammatory adipocytokines expression with high-fat-diet induced obese mice. Chow-diet (CD) mice and high-fat-diet (HFD) mice were fed with 10% kcal% fat and 45% kcal% fat (Research Diet D12450J, D12451) post weaning, respectively. Pain responses to mechanical and thermal stimuli were recorded at age of 6, 8, 10, 12 weeks, together with body weight and glucose, triglyceride, cholesterol in blood. Then lumbar spinal cords were collected at the age of 12 weeks when the HFD mice overweighed the CD mice by 30% in average. Hypersensitivity to von Frey hairs was recorded at the age of 12 weeks in the HFD mice, while no difference with responses to heat stimulation. Microglia (recognized by Iba1) and astrocytes (recognized by GFAP) became activated in the spinal cord from the obese mice with increased fluorescence intensity and morphological changes identified by immunohistochemistry, while no statistical difference for the levels of Iba1 and GFAP using western blotting between the HFD mice and CD mice. mRNA expression of proinflammatory adipocytokines including IL-1β, IL-6, IL-8, TNF-α, and MCP-1 in spinal cord and plantar tissue were significantly upregulated in the HFD mice. In conclusion, the proinflammatory adipocytokines level increased with obesity, together with glial activation and hypersensitivity to mechanical stimulation. Further investigation will be needed to understand the connection between neuroinflammation, glial activation and hypersensitivity to nociceptive stimulation in HFD mice.

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Poster

810. Neuroinflammation: Cellular mechanisms

Location: Hall A

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: Veterans Administration Merit Review grant-NEUD-004-07F

Title: Microglial inflammasome formation in obese and diabetic models

Authors: *S. PUGAZHENTHI[1], A. TYAGI[2];
[1]Res. Services-151, Denver VA Med. Ctr., Denver, CO; [2]Med., Univ. of Colorado, Aurora, CO

Abstract: Inflammasome, a multiprotein cytosolic complex, is generated in response to infection, cellular damage and metabolic dysregulation. Its formation leads to activation of caspase-1, followed by proteolytic cleavage and secretion of IL-1β and IL-18. Cellular stress-induced sterile inflammasome formation sets in motion the vicious cycle of neuroinflammation, a central player in cognitive decline of the aging population. A growing number of studies have reported that obesity in mid-life is a predictor of mild cognitive impairment in old age. Brain inflammation in obese individuals is being considered as secondary to peripheral inflammation originating from macrophages. The possibility of microglial activation in response to saturated fatty acids has not been fully investigated although this pathway in hypothalamus is documented. Increased fatty acid uptake by the brain in metabolic syndrome has been demonstrated. To determine the mechanism of central inflammation in obesity and diabetes, we performed pathway specific gene expression profiling with hippocampal samples of mice fed high fat diet for 5 months and of Zucker diabetic rats, a model for type 2 diabetes. Significant elevation of several oxidative stress pathway genes including iNOS, regulatory protein for NOX enzymes (p41NOX), dual oxidase-1, and myeloperoxidase was observed. The inflammatory pathway genes induced were GM-CSF, a growth factor that increases the proliferation of microglia, IFN-γ, P-Selectin, E-Selectin, CCL4, CCL6, CCL7 and CXCL10. Immunoblot analysis revealed the cleavage of caspase-1 and IL-1 beta in these brain samples. Cultured BV cells, a mouse microglial cell line, exposed to palmitic acid secreted IL-1β, a marker for inflammasome formation which was inhibited by caspase-1 inhibitor. Mitochondrial respiration measured by high resolution respirometry using Oroboros Oxygraph-2k decreased in these cells. The combination of obesity and type 2 diabetes (T2D) is a serious health problem, which is projected to afflict 300 million people worldwide by 2020. While improved glycemic control has extended the life span of diabetic patients, it has revealed their susceptibility to aging-associated cognitive decline. Cognitive dysfunction and decrease in brain volume has been reported in chronic T2D patients. While studies in obesity research have focused on macrophages of the periphery, microglial activation of the CNS has remained mostly in the domain of Alzheimer's research. Our findings could bridge these two domains to develop a consensus approach to reduce inflammation in periphery and CNS in aging-associated disorders.

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Poster

810. Neuroinflammation: Cellular mechanisms

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

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Sandler Foundation

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Title: Role of exosomes in microglia communication and inflammation

Authors: *J. C. UDEOCHU[1], S. VILLEDA[2];
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Abstract: Microglia, the resident immune cells of the brain, have an important role in maintaining homeostasis through constant surveillance of the brain parenchyma. This homeostatic function is facilitated by the ability of microglia to rapidly sense and respond to physiological and pathological alterations. Although cytokines, purines, and trophic factors have been implicated in microglia responses, it is unclear what other mediators of communication are used by microglia. Bulk transfer of protein, RNA and lipid cargo, via membrane bound extracellular vesicles (EVs), has recently emerged as a conserved mode of cell communication in various cell types. Seminal work in this field has established exosomes, 30-150nM sized EVs, as regulators of activation and cytokine production in peripheral mononuclear cells (PMCs). While there is evidence for microglia exosome secretion, it is unclear if exosome transfer mediates intercellular communication in microglia. Thus, we hypothesized that bulk transfer of protein and RNA message via exosomes plays an important role in microglia-microglia communication and inflammatory activation. We have used a combination of *in vitro* and *in vivo* approaches to characterize microglia-derived exosomes and microglia responses to exosome stimulation. Exosomes were purified from media of primary mouse microglia and BV2 microglia cell line cultures, and characterized for stereotypical morphology and size using electron microscopy and nanoparticle tracking analysis. The functional role of exosome-mediated communication was investigated by examining changes in the ability of microglia to phagocytize opsonized latex beads after exposure to exosomes *in vitro*. We detected that exosome stimulation of microglia significantly enhances microglia phagocytosis. Correspondingly, analysis of microglia-derived exosomes by mass spectrometry identified various proteins implicated in phagocytosis. Additionally, exosome stimulation increased gene expression of inflammatory mediators such as IL1β and TNFα in microglia. Interestingly, total cellular mRNA levels were also reduced in exosome-stimulated groups relative to control, raising the prospect of exosome-RNA mediated transcriptional repression. Ongoing experiments are focused on elucidating mechanisms underlying the observed phagocytic enhancement and transcriptional repression in exosome-stimulated microglia. Together, our data indicate that bulk transfer of protein and RNA via exosomes regulates phagocytosis and inflammatory responses in microglia, positioning exosome-mediated communication as a critical regulator of physiological processes in microglia.

Disclosures: **J.C. Udeochu:** None. **S. Villeda:** None.

Poster

810. Neuroinflammation: Cellular mechanisms

Location: Hall A

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Program#/Poster#: 810.11/X7

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

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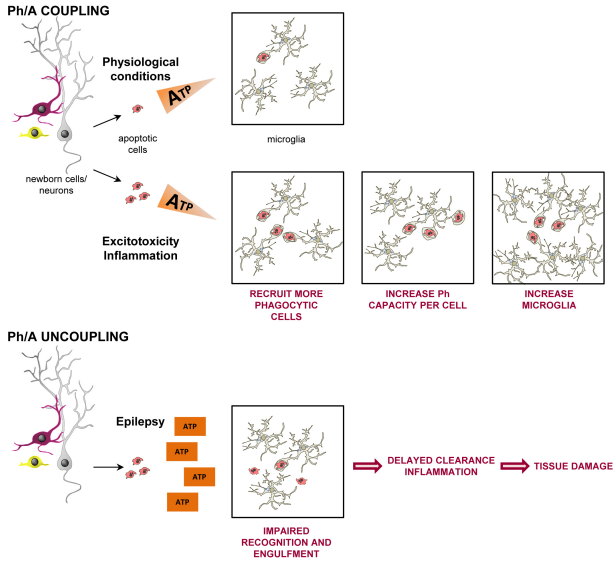
Title: Neuronal hyperactivity disturbs ATP microgradients and triggers apoptosis/microglial phagocytosis uncoupling

Authors: O. ABIEGA[1], S. BECCARI[1], I. DIAZ-APARICIO[1], A. NADJAR[2], S. LAYÉ[2], Q. LEYROLLE[2], D. GÓMEZ-NICOLA[3], M. DOMERCQ[1], A. PÉREZ[1], V. SÁNCHEZ-ZAFRA[1], I. PARIS[1], J. J. DEUDERO[4], A. L. BREWSTER[4], A. E. ANDERSON[4], L. ZALDUMBIDE[5], L. GALBARRIATU[5], A. MARINAS[5], M. D. VIVANCO[6], C. MATUTE[1], M. MALETIC-SAVATIC[4], J. M. ENCINAS[1,7,8], *A. SIERRA[1,7,8];
[1]Achucarro Basque Ctr. For Neurosci., Zamudio, Spain; [2]Univ. Bordeaux Segalen,, Bordeaux, France; [3]Ctr. for Biol. Sciences, Univ. of Southampton, Southampton, United Kingdom; [4]The Jan and Dan Duncan Neurolog. Res. Inst. at Texas Children's Hosp., Baylor Col. of Med., Houston, TX; [5]Cruces Univ. Hosp., Bilbao, Spain; [6]CIC BioGUNE, Derio, Spain; [7]Ikerbasque Fndn., Bilbao, Spain; [8]Univ. del País Vasco EHU/UPV, Leioa, Spain

Abstract: Phagocytosis is an essential component of the brain regenerative response that remains poorly explored. We have discovered a universal response of surveillant, ramified

microglia to apoptotic challenge induced by inflammation or excitotoxicity *in vitro* and *in vivo*. Microglia resorted to different strategies to boost their phagocytic output and compensate for the increased number of apoptotic cells, thus maintaining phagocytosis and apoptosis tightly coupled. Unexpectedly, this coupling was chronically lost in a experimental and human mesial temporal lobe epilepsy (MTLE), a major neurological disorder characterized by seizures, excitotoxicity, and inflammation. Importantly, the phagocytosis/apoptosis uncoupling correlated with the expression of microglial pro-inflammatory, epileptogenic cytokines, suggesting its contribution to the pathophysiology of epilepsy. The phagocytic blockade was not directly mediated by glutamate receptors on microglia but by the disruption of local ATP microgradients caused by the hyperactivity of the hippocampal network, which reduced microglial motility and surveillance, and prevented the efficient targeting of apoptotic cells. Finally, the uncoupling led to an increase in the number of apoptotic newborn cells in the neurogenic niche that was not due to decreased survival but to delayed cell clearance after seizures. These results demonstrate that the efficiency of microglial phagocytosis determines the dynamics of apoptosis, and urge to routinely assess the microglial phagocytic efficiency in neurodegenerative disorders.



Disclosures: **O. Abiega:** None. **S. Beccari:** None. **I. Diaz-Aparicio:** None. **A. Nadjar:** None. **S. Layé:** None. **Q. Leyrolle:** None. **D. Gómez-Nicola:** None. **M. Domercq:** None. **A. Pérez:** None. **V. Sánchez-Zafra:** None. **I. Paris:** None. **J.J. Deudero:** None. **A.L. Brewster:** None. **A.E. Anderson:** None. **L. Zaldumbide:** None. **L. Galbarriatu:** None. **A. Marinas:** None. **M.D. Vivanco:** None. **C. Matute:** None. **M. Maletic-Savatic:** None. **J.M. Encinas:** None. **A. Sierra:** None.

Poster

811. Neuroimmunology: Behavioral Effects

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 811.01/X8

Topic: E.02. Neuroimmunology

Support: OSU Startup Funds to KML

Title: Mast cells and maternal allergy regulate early life programming of offspring social, affective and hyperactive behavior

Authors: *K. M. LENZ[1,2,3], S. PLATKO[2], A. GALAN[1];
[1]Psychology, [2]Neurosci., [3]Group in Behavioral Neuroendocrinology, The Ohio State Univ., Columbus, OH

Abstract: Perinatal inflammation increases risk for neurodevelopmental disorders, including autism, schizophrenia and ADHD. Autism and ADHD are four times more common in males than females, and there are significant sex differences in onset, severity, and symptoms of schizophrenia. We aim to understand how sex differences in the brain's innate immune environment regulates sex-specific brain development, and ultimately, sex-specific programming of behavior by inflammatory events. Mast cells are innate immune cells, largely associated with peripheral allergy, that are present in the brain of both rodents and humans. Mast cells secrete serotonin, histamine and cytokines, yet their role in brain development is unknown. We have found that thousands of mast cells reside in the developing rat brain, with over 90% situated in or near the hippocampus, thalamus, and amygdala. Males have 40% more mast cells in the brain than females during the neonatal period; by adulthood both males and females have only a few hundred brain-resident mast cells. The goal of these experiments was to determine whether the mast cell population in the neonatal brain regulates the development of social behavior, mood, and impulsivity/attention that are impacted in many neurodevelopmental disorders. We induced mast cell activation during development using prenatal allergic immune challenge on embryonic day 15, and found that it led to significantly increased total mast cells and the percent of activated mast cells in the brains of pups, effects that persisted to postnatal day 4. We then tested juveniles and adults on various behavioral tasks, beginning with juvenile social play behavior post-weaning, which shows a significant sex difference (males > females) at baseline. Males that experienced allergic challenge *in utero* engaged in less social play behavior than control males; in contrast, allergic challenge females showed increased social play behavior relative to control females, indicative of a masculinized phenotype. On the open field test, both allergic challenge males and females showed increased time in the center in the open field than controls and increased locomotion, indicating decreased anxiety and hyperactivity. Currently underway experiments will determine the effects on allergic challenge on adult social interaction, social memory, and attention, as well as assessing the effects of allergic challenge on immediate early

gene expression throughout the limbic system. Together these studies show that mast cells may play a key role in the early life programming of sex differences in brain and behavior following early life perturbations.

Disclosures: K.M. Lenz: None. **S. Platko:** None. **A. Galan:** None.

Poster

811. Neuroimmunology: Behavioral Effects

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 811.02/X9

Topic: E.02. Neuroimmunology

Title: Effects of the oxytocin agonist, carbetocin, on sickness behaviours and immune responses in male mice

Authors: *J. M. DELEEMANS, K.-P. OSSENKOPP, M. KAVALIERS;
Dept. of Psychology, Western Univ., London, ON, Canada

Abstract: The nonapeptide, Oxytocin (OT), is implicated in the modulation of reproductive functions and social behaviours, and has also been shown to influence stress response and immune system function. The present study investigated effects of the OT agonist, carbetocin, on behavioural responses and pro-inflammatory cytokine function associated with sickness behaviour in adult male CD-1 mice. To evaluate whether OT is involved in the onset of an immune response and expression of sickness behaviours, adult male mice received either a low (10mg/kg) or high (20mg/kg) intraperitoneal injection of carbetocin, followed 15 minutes later by either saline vehicle or 75μg/kg lipopolysaccharide (LPS), a bacterial endotoxin mimetic, to initiate an immune response. Mice were then tested for 30 minutes in a Dark-Light paradigm to assess locomotor and anxiety related behaviours. Following behavioural testing, animals were euthanized and blood samples were collected for later measurement of Tumor Necrosis Factor Alpha. Mice displayed sickness-like behaviours as shown by reduced locomotor activity and increased anxiety, indicated by increased time spent in the dark chamber, along with reduced number of Dark-Light transitions. The behavioural data showed that OT did not attenuate sickness behaviours in mice treated with LPS. However, in mice treated with carbetocin and then saline, anxiety-like behavior was attenuated and exploratory locomotor activity was augmented, which is consistent with previous studies showing that OT has anxiolytic effects. These results suggest that in male mice carbetocin does not suppress acute phase anxiety and locomotor related sickness behaviours, with immune measures pending.

Disclosures: **J.M. Deleemans:** None. **K. Ossenkopp:** None. **M. Kavaliers:** None.

Poster

811. Neuroimmunology: Behavioral Effects

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 811.03/X10

Topic: E.02. Neuroimmunology

Support: NIH Research Scientist Career Development Award (K01DK100616)

Medical College of Georgia, Medical Scholars Program

Title: Reversibility of neuroinflammation and impaired hippocampal function in high fat diet-induced obesity

Authors: ***A. DEY**[1,2], S. HAO[1,2], A. M. STRANAHAN[1];
[1]Neurosci. and Regenerative Med., [2]Med. Col. of Georgia, Georgia Regents Univ., Augusta, GA

Abstract: Obesity increases rates of age-related cognitive decline and dementia, but the mechanisms have yet to be identified. In rodents, high-fat diet consumption (HFD) is associated with deficits in hippocampal function and inflammation in the central nervous system, but basic questions surrounding these processes have yet to be addressed. Specifically, the question of whether consumption of a low-fat diet (LFD) reverses brain inflammation in dietary obesity has never been examined, and as a consequence, the reversibility of cognitive and synaptic deficits remains open to speculation. In this study, we examined the metabolic, neuroimmune, and cognitive consequences of diet reversal. Male mice were fed HFD for 3 months, which was the earliest time point when neuroinflammation and synaptic dysfunction were detected in pilot studies. Half of the HFD mice were then switched to LFD (HFD/LFD) for an additional 2 months, or continued to consume HFD throughout this period (HFD/HFD). An additional set of mice were maintained on LFD throughout the experiment (LFD/LFD). HFD/LFD mice had lower body weights than HFD/HFD mice, but analysis of fat pad weights revealed that HFD/LFD mice still exhibit greater adiposity relative to LFD/LFD mice. Inflammation in visceral adipose tissue was evident in HFD/HFD mice based on immunohistochemical detection of macrophage markers in the epididymal fat pads and analysis of proinflammatory cytokines in adipose tissue using western blotting and ELISA. HFD/HFD mice also had elevated levels of circulating inflammatory cytokines, including TNFa and IL1b. Diet reversal attenuated macrophage accumulation and inflammatory cytokine expression in epididymal fat from HFD/LFD mice, and reduced circulating levels of TNFa and IL1b. HFD/HFD mice had more

cells that expressed the microglial marker IBA1, and many IBA1-positive cells co-expressed MHCII, a marker of classical activation. Diet reversal prevented increases in the number of hippocampal microglia and blocked induction of MHCII in IBA1-positive cells. Attenuation of local inflammation in the hippocampus of HFD/LFD mice was accompanied by normalization of dentate gyrus long-term potentiation (LTP), dendritic spine density, and spatial recognition memory. Taken together, these findings indicate that dietary obesity reversibly impairs hippocampal function, and that synaptic deficits may be attributable to microglial activation. Future studies will be needed to identify the signaling mechanisms for reinstatement of hippocampal function with diet reversal, and to determine whether synaptic deficits and neuroinflammation in obesity are interrelated or independent processes.

Disclosures: **A. Dey:** None. **S. Hao:** None. **A.M. Stranahan:** None.

Poster

811. Neuroimmunology: Behavioral Effects

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 811.04/X11

Topic: E.02. Neuroimmunology

Title: Inflammation induces changes in the reward system through a prostaglandin dependent and a prostaglandin independent mechanism

Authors: M. A. SOTOMAYOR[1], *C. GOMEZ[1], A. OCHOA[1], *C. GOMEZ[3], M. D. PÉREZ[2], L. A. MÉNDEZ[2], J. A. LÓPEZ[4];
[2]Pharmacol., [1]Natl. Univ. Mexico, Mexico, Mexico; [3]Med., La Salle Univ., Mexico, Mexico; [4]Natl. Inst. of Psychiatry, Mexico, Mexico

Abstract: The field of neuro-immunology provides new insight into the function of the nervous system, linking inflammation to depression and neurodegeneration among others, however the precise relationship has not been completely determined. The aim of this study was to explore the influence of peripheral inflammatory processes over the response of the reward system to pharmacological and nutritional reinforcers. Place preference: We tested the reinforcement of morphine in the place preference model, in a 3 compartment box with different color and textures, time spent by the animal in each compartment was assessed before, and after 4 conditioning sessions in which a compartment was paired with morphine, while the other one was paired with saline, time spent after conditioning sessions minus time spent before conditioning sessions was calculated. After habituation the animal was subjected to deafferentation of the right hind paw, a week later conditioning sessions with a subcutaneous

administration of morphine (5 mg/kg) began (control group). Peripheral inflammation group: The same as control group, but 24 hours previous to conditioning sessions, carrageenan (carr) 750µl was injected in the denervated paw. Pharmacological modulation of inflammation: The same as the inflammation group, but after carrageenan injection the animal received ibuprofen (ibu) 0.6mg/ml in the drinking water, and 15 minutes prior to conditioning sessions ibu 50mg/kg, i.p. Rats develop a significant place-preference for the morphine paired side ($p=0.001$) with an average increase of 174 seconds (sec), rats that were pretreated with the inflammatory stimuli did not show this place preference with an average increase of 11.6 sec ($p=0.003$); when we administered ibu (a prostaglandin synthesis blocker), the animals didn't only recovered the reward response, but it was greatly increased with an average of 497.7 sec ($p<0.005$). Two bottle choice: Two groups of rats with prior deafferentation of the right hind paw, one without any inflammatory stimulus, the other with an intraplantar injection of carr 750µl, had free access to two bottles, one with tap water, the other one with tap water plus saccharine 4mmol; total liquid consumption and percentage of tap water vs saccharine (sac) water were measured for 11 days. Rats had a significative decrease in sac water consumption inversely correlated with paw diameter (Pearson test=-0.55), this decrease was reverted as the inflammatory process was resolved (the paw diameter returned to normal). The evidence above suggests that inflammatory stimulus inhibit the reward response to pharmacological and nutritional rewards by a prostaglandin-mediated pathway.

Disclosures: **M.A. Sotomayor:** None. **A. Ochoa:** None. **C. Gomez:** None. **M.D. Pérez:** None. **L.A. Méndez:** None. **J.A. López:** None.

Poster

811. Neuroimmunology: Behavioral Effects

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 811.05/X12

Topic: E.02. Neuroimmunology

Title: Associations between polymorphisms in immune-related genes and autistic-like traits in a Swedish population

Authors: ***N. STRENN**[1], D. HOVEY[1], L. JONSSON[1], H. ANCKARSÄTER[2], P. LICHTENSTEIN[3], A. EKMAN[1];
[1]Pharmacol., Sahlgrenska Acad., Gothenburg, Sweden; [2]Dept. of Forensic Psychiatry, Sahlgrenska Academy, Univ. of Gothenburg, Gothenburg, Sweden; [3]Dept. of Med. Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

Abstract: Background: Autism spectrum disorders are a complex group of neurodevelopmental disorders which are characterized by impairments in social interactions and both verbal and nonverbal communication as well as by unusual repetitive behaviour. The immune system has been suggested to be of importance for the development of neuropsychiatric symptoms; for example, elevated levels of cytokines and the inflammation-related transcription factor nuclear factor kappa-B (NFKB) have been reported in both blood and brain tissue of autistic individuals. Objectives: The aim of this study was to investigate possible associations between single nucleotide polymorphisms (SNPs) in several immune-related genes, amongst others, NFKB and NFKB inhibitor-like protein 1 (NFKBIL1) and autistic-like traits in a Swedish population of twins. Methods: The subjects in this study (n=12426, 9-12 years old) are from "The Child and Adolescent Twin Study in Sweden" (CATSS). Their parents participated in a telephone interview where the children were assessed by the Autism-Tics, ADHD, and Other Comorbidities Inventory (A-TAC) where autistic-like traits are measured using a continuous scale. DNA was extracted from saliva samples and polymorphisms were genotyped. Statistical analyses were performed in the SAS 9.3 (SAS Institute, Inc., Cary, NC) softwear. Results: Four out of the five investigated SNPs (NFKB: rs4648022; NFKBIL1: rs2230365, 2239707 and rs2857605) showed significant associations with the A-TAC total autistic-like traits score. Conclusions: To our best knowledge, polymorphisms in the genes encoding NFKB and NFKBIL1 have not previously shown to be associated with autism. These proteins may be involved in neuronal development and our findings support the hypothesis of the immune system being important in the aetiology of neuropsychiatric symptoms.

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Poster

811. Neuroimmunology: Behavioral Effects

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 811.06/X13

Topic: E.02. Neuroimmunology

Title: Role of astrocytic GABAergic system on inflammatory cytokine-induced depressive-like behavior

Authors: *H. SHIM[1], H.-J. PARK[2], K. KIM[3], D.-H. HAHM[4], H. LEE[5], I. SHIM[4];
[1]Grad. School, Col. of Korean Medicine, Kyung Hee Univ., Seoul 137-701, Korea, Republic of; [2]Bringham Young Univ., Provo, UT; [3]Dept. of Integrative Med. and Res. Ctr. of Behavioral

Medicine, Col. of Medicine, The Catholic Univ. of Korea, Seoul, Korea, Republic of; [4]Acupuncture and Meridian Sci. Res. Center, Col. of Korean Medicine, Kyung Hee Univ., Seoul, Korea, Republic of; [5]Korea Inst. of Oriental Med., Daejeon, Korea, Republic of

Abstract: Backgrounds: Recent studies have shown that not only neurons but astrocytes contain a considerable amount of γ-aminobutyric acid (GABA), which can be released and activate the receptors responsive to GABA. GABA from reactive astrocytes has been implicated in epilepsy, sleep, memory and cognition. The mechanism underlying the astrocytic release of GABA in depression is poorly understood. The purpose of this study is to test whether gliotransmitters from astrocytes may play a role in etiology of depressive-like symptoms.**Methods:** After rat recombinant IL-1β was infused into 3rd ventricle (100 ng, ICV) or paraventricular nucleus (10 ng, i.PVN) of the hypothalamus (PVN), the rats were tested for depressive-like behaviors in elevated plus maze, open field test and tail suspension test. Expression of glial fibrillary acidic protein (GFAP) and GABA were investigated using the immunofluorescence. Next, the systemic or intracerebral injections of L-α-aminoadipate (L-AAA, 0.5, 5 mg/rat, s.c. or 250 nmol/μL/bilateral into the PVN), a specific astrocyte toxin or bestrophin-1 channel blocker 5-Nitro-2-(3-phenylpropylamino) benzoic acid; (NPPB, 40 mg/kg, i.p. or 300 nmol/μL/bilateral in to the PVN) was pretreated before IL-1β ICV or i.PVN injection and depressive-like behaviors and GABA and GFAP expression in the PVN were measured. Finally, extracellular GABA release was measured using *in vivo microdialysis* in order to examine the role of astrocytic GABA in IL-1β induced depressive behaviors.**Results:** I.c.v infusion of IL-1β (100ng) induced depressive-like behaviors and activated the glial fibrillary acidic protein (GFAP) in the PVN and hippocampal dentate gyrus (DG). However, astrocyte inhibition by systemic L-AAA reduces depressive behaviors and the GFAP expression in the PVN. Injection of IL-1β (10ng) into the PVN produced markedly depressive behaviors and increased release of GABA from astrocyte. Local injection of L-AAA or blockade of Best1 channel by systemic NPPB, specific Best1 channel blocker, decreased depressive behaviors, but not changed the GABA expression in the PVN. Finally, IL-1β injection into the PVN release GABA measured by *in vivo microdialysis,* and treatment of L-AAA or NPPB decreased IL-1β-induced gliotransmitter GABA release. **Conclusion:** The present results demonstrated that release of gliotransmitter GABA in the brain may modulate the interleukin 1β-induced depressive responses. These results suggest that selective inhibition of astrocyte or astocytic GABA release may serve as an effective therapeutic strategy for treating depression.

Disclosures: H. Shim: None. **H. Park:** None. **K. Kim:** None. **D. Hahm:** None. **H. Lee:** None. **I. Shim:** None.

Poster

811. Neuroimmunology: Behavioral Effects

Location: Hall A

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Program#/Poster#: 811.07/X14

Topic: E.02. Neuroimmunology

Support: PHS MH104800

PHS NIEHS P30 ES022

NIH-ES07148

Title: T cell maternal immune activation leads to deficits in prepulse inhibition and sex-specific deficits in spatial learning in adult offspring

Authors: ***N. W. FOX**, H. M. DEITCH, Z. S. WITTER, A. W. KUSNECOV;
Rutgers Univ., Piscataway, NJ

Abstract: Prenatal maternal immune activation (MIA) is a risk factor for several psychopathologic disorders, including bipolar disorder, autism, and schizophrenia. Most research has focused on using toll-like receptor (TLR) agonists such as lipopolysaccharide (LPS) or the synthetic viral genome analogue polyinosinic:polycytidylic acid (poly I:C) as experimental immune activators. Little is known about how T cells, necessary for successful clearance of both viruses and intracellular bacteria, may influence the neurodevelopment of a gestating fetus. To this end, we challenged pregnant female C57Bl/6J mice on day E12.5 of gestation with 200 ug/kg of purified staphylococcal enterotoxin A (SEA) to oligoclonally activate maternal T cells. After successful birth and weaning, both male and female adult offspring (N = 7-12 / sex / treatment) from SEA and Saline-treated mothers were tested for spatial navigation in a water radial arm maze (wRAM) and for deficits in acoustic sensorimotor gating, as measured by prepulse inhibition (PPI). In the wRAM, after eight days of hidden platform training, female offspring from SEA mothers took significantly longer to find the escape platform ($F(1, 83) = 6.50$, $p < 0.05$). Females from SEA mothers also swam further prior to reaching the platform ($F(1, 83) = 3.68$, $p = 0.058$). There were no differences in swim speed between SEA treatment and control animals. For male offspring, there was no observed difference in either swim distance or latency to find the escape platform, though males from SEA-treated mothers swam significantly slower ($F(1, 149) = 6.17$, $p < 0.05$). When these offspring were tested for PPI, offspring from SEA mothers had less percent inhibition over two days of testing ($F(1, 27) = 5.36$, $p < 0.05$), suggesting a stable deficit in sensorimotor gating due to maternal immune challenge with SEA. These data suggest that specific T cell activation during pregnancy compromises neurobehavioral development of the offspring. Acknowledgements: Supported by PHS grants MH104800 and NIEHS P30 ES022, NIH-ES07148.

Disclosures: **N.W. Fox:** None. **H.M. Deitch:** None. **Z.S. Witter:** None. **A.W. Kusnecov:** None.

Poster

811. Neuroimmunology: Behavioral Effects

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Program#/Poster#: 811.08/X15

Topic: E.02. Neuroimmunology

Support: NIA grant R00AG040194

Alzheimer's North Carolina Inc.

Title: Temporal changes in LPS-induced microglial cell activation in adult and aged mice

Authors: *R. A. KOHMAN, A. M. LITTLEFIELD, S. E. SETTI, P. R. FREEMAN; Psychology, Univ. of North Carolina Wilmington, Wilmington, NC

Abstract: The brain's resident immune cells, microglia, can express distinct forms of activation including the classic pro-inflammatory (M1) and alternative anti-inflammatory and neuroprotective (M2) phenotypes. Prior work has shown that at distinct time-points after a stroke or traumatic brain injury microglia express different phenotypes, indicating a time-dependent shift in activation (Hu et al., 2012; Wang et al., 2013). Further, normal aging has been shown to prime microglia towards the M1 phenotype. As a result, aged subjects show an abnormal neuroinflammatory response to an immune challenge when compared with adults. Presently unknown is how these age-related changes in microglia activation differ across time. The current study evaluated whether adult and aged mice show differential temporal profiles of microglia activation following an immune challenge. Aged (18-20 months) and adult (6-5 months) female C57BL6/J mice were administered a single intraperitoneal injection of the bacterial endotoxin lipopolysaccharide (LPS) or saline. Alterations in locomotor and anxiety-like behavior were assessed 1, 2, 3, or 7 days following LPS or saline exposure. Immediately following behavioral testing, hippocampal samples were collected. Hippocampal expression of genes associated with the M1 and M2 microglia phenotypes is currently in progress. Preliminary data indicate that aged mice show prolonged behavioral deficits following LPS administration relative to adult mice. We predict that aged mice will show prolonged LPS-induced expression of proinflammatory cytokines relative to adults, in agreement with prior reports. Further, the current data will determine whether the onset and duration of an anti-inflammatory response is altered in aged subjects.

Disclosures: R.A. Kohman: None. **A.M. Littlefield:** None. **S.E. Setti:** None. **P.R. Freeman:** None.

Poster

811. Neuroimmunology: Behavioral Effects

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 811.09/X16

Topic: E.02. Neuroimmunology

Title: Behavioral phenotyping of male and female IL1-R1 null mutant mice reveals sex-specific impairments in the Morris Water Maze and Porsolt Forced Swim Test

Authors: *J. A. JOHNSON[1], S. N. RESCH[1], A. PEREZ[1], S. D. CROLL[2,3];
[1]Clin. Neuropsychology, CUNY Grad. Ctr., New York, NY; [2]Pain, Addiction, and Neurol., Regeneron Pharmaceuticals, Tarrytown, NY; [3]Psychology, CUNY Queens Col., Flushing, NY

Abstract: IL1-R1 null mutant mice (IL1-R1 KO) have reduced signaling in the interleukin-1 (IL-1) pathway, making them a convenient model for testing the importance of IL-1 in either the development or maintenance of mouse behaviors. Prior research has revealed impaired cognitive and emotional processes in adult male IL1-R1 KO mice, including impaired spatial learning and memory and decreased anxiety. We tested both male and female IL1-R1 KO animals and wild-type (WT) animals on an array of behavioral tests, including retesting at an older age for spatial learning and memory. Animals were sacrificed and their brains were measured for neuroanatomical abnormalities and differences in hippocampal vascular investment. Our findings were consistent with prior findings of impaired spatial learning and memory performance for male IL1-R1 KO animals, as well as reduced anxiety-type responses in multiple behavioral tests. Female IL1-R1 KO mice were less affected, and showed no behavioral impairment in the Morris Water Maze. We found increased depressive-type behavior in the Porsolt Forced Swim test, but only in female IL1-R1 KO animals. All animals were retested at a later age in the MWM to determine if the observed sex-based differences in impaired spatial learning and memory would persist or increase with age. We found impaired spatial memory performance for aged IL1-R1 KO animals, and although older male KOs showed poorer performance in the water maze than female KOs, the difference between sexes no longer achieved statistical significance. Neuroanatomical evaluation revealed no gross differences in cortical or hippocampal structure. However, IL1-R1 KO animals had significantly reduced vascular investment in the hippocampal region, a finding that significantly correlated with impaired spatial memory performance in older animals ($r = .535$, $p = .027$). Our findings suggest that disruption of normal IL-1 activity can influence vascular density in the hippocampus and also alter hippocampally-mediated behavior, including spatial learning and memory. Our findings also reveal sex-dependency of these effects,

suggesting the possibility that male and female animals suffer different behavioral consequences of IL-1 signaling deficiency.

Disclosures: **J.A. Johnson:** None. **S.N. Resch:** None. **A. Perez:** None. **S.D. Croll:** A. Employment/Salary (full or part-time):; Regeneron Pharmaceuticals.

Poster

811. Neuroimmunology: Behavioral Effects

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: E.02. Neuroimmunology

Support: Olle Engkvist Byggmästare Foundation

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Swedish Foundation for Strategic Research

Berzelii Centre Stockholm Brain Institute (Vinnova & Swedish Research Council)

Strategic Research Program in Neuroscience at Karolinska Institutet

Title: Increased social approach in adult mice raised under germ-free conditions: Implications for neurodevelopmental disorders

Authors: *H. RAITH, T. ARENTSEN, Y. QIAN, R. DIAZ HEIJTZ;
Karolinska Institutet, Stockholm, Sweden

Abstract: Environmental influences during early life can have a profound impact on brain development and later life structure and function. One such environmental factor is the gut microbiota (the microorganisms that inhabit our intestines) that over evolutionary time has adapted to coexist with mammals. A growing number of studies have recently revealed that the gut microbiota has much wider effects on host physiology and development than originally believed, including the developmental programming of brain and later-life behavior. We have previously shown that adult NMRI mice raised under germ-free (GF) conditions display increased motor activity and decreased anxiety-like behavior compared to mice with normal gut microbiota (specific-pathogen-free, SPF). To further access the influence of the gut microbiota on social approach behavior, we subjected adult GF and SPF Swiss-Webster mice to a three-chambered sociability approach test. In addition, we included other tests for motor activity and

anxiety-like behavior that were used in our previous studies with NMRI mice. In the present study, we demonstrate that adult Swiss-Webster mice display increased sociability, as well as increased motor activity and reduced anxiety-like behavior compared to Swiss-Webster SPF mice. These mice also show alterations in the expression of synaptic-related plasticity molecules (e.g. BDNF) in key regions involved in social behavior (e.g., amygdala). Our results suggest that the postnatal microbial colonization process initiates signaling mechanisms that affect neuronal circuits involved in social behavior, motor control and emotional responses.

Disclosures: **H. Raith:** None. **T. Arentsen:** None. **Y. Qian:** None. **R. Diaz Heijtz:** None.

Poster

811. Neuroimmunology: Behavioral Effects

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 811.11/X18

Topic: E.02. Neuroimmunology

Support: Start-up Funding from the University of Dayton

Title: Lipopolysaccharide administration induces sustained sex-dependent monoaminergic neurochemical alterations in the mouse brain

Authors: *J. P. SENS, E. SCHNEIDER, E. BIRMINGHAM, J. MAUCH, A. FRANCESCHELLI, C. THELEN, P. M. PITYCHOUTIS;
Dept. of Biol. & Ctr. for Tissue Regeneration and Engin. (TREND), Univ. of Dayton, Dayton, OH

Abstract: The innate immune response is an important component of the immune system that serves to isolate and prevent further infection from pathogenic organisms. A component of the response manifests as sickness symptoms (i.e. decreased locomotor activity, anorexia) and depressive-like neurobehavioral outcomes (i.e. anhedonia, social withdrawal, alterations in central monoaminergic neurotransmission) that are prefaced by complex immune-to-brain communication pathways that ultimately result in proinflammatory cytokine production within the brain. Indeed, patients that suffer from chronic inflammatory diseases, such as rheumatoid arthritis, have an increased risk of developing major depression. Despite the greater prevalence of major depression in women, the role of sex in the neuroimmunology of depression remains elusive. Of note, the proinflammatory agent lipopolysaccharide (LPS) has been shown to activate the innate immune machinery that leads to depressive-like neurobehavioral alterations in rodents. Herein, we investigated whether acute immune stimulation with LPS induces sex-dependent

serotonergic and dopaminergic neurochemical responses in limbic brain regions implicated in the pathophysiology of major depression, namely the prefrontal cortex (PFC), the hippocampus (HIPP), the amygdala (AMY) and the striatum (STR). Mice were injected with LPS (0.83 mg/kg) or saline (0.9% NaCl), and were sacrificed at two different time-points; at 6h (i.e. when sickness symptoms reach their plateau) and at 24h post-LPS administration (i.e. when sickness symptoms are alleviated but depressive-like symptoms are still evident). *Ex vivo* neurochemical responses were assayed with high performance liquid chromatography (HPLC) with coulometric detection. Collectively our data showed that LPS administration induced sex-dependent serotonergic and dopaminergic neurochemical effects at both time-points. Our efforts now focus on how these neurobiological alterations ultimately play out in an effect on basic behavior. With a higher prevalence of affective disorders in women, an understanding of the neurobiological mechanisms of sex differences underlying this inflammatory model of depression is imperative to delineate the neuroimmunological substrate in the appearance, course and outcome of these conditions.

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Poster

811. Neuroimmunology: Behavioral Effects

Location: Hall A

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Program#/Poster#: 811.12/X19

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NARSAD

NIH Grant MH094527

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Title: Conditional elimination of p38α mitogen activated protein kinase provides evidence for a cell autonomous role of kinase signaling in SERT regulation and serotonin-linked behaviors following immune system activation

Authors: *N. L. BAGANZ[1,2], K. L. LINDLER[1], C. B. ZHU[3], J. T. SMITH[1], M. J. ROBSON[1], H. IWAMOTO[1], E. DENERIS[5], W. A. HEWLETT[6], R. D. BLAKELY[1,4,2];
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Med. Ctr., Nashville, TN; [5]Neurosci., Case Western Reserve Univ., Cleveland, OH; [6]Inst. for Psychiatric Neurosci., Nashville, TN

Abstract: Central serotonin (5-HT) neurotransmission and peripheral immune system activation have been linked to multiple neuropsychiatric disorders, including depression, anxiety, schizophrenia and autism. The antidepressant-sensitive 5-HT transporter (SERT, SLC6A4) is a critical determinant of synaptic 5-HT inactivation and is tightly regulated by multiple signaling pathways, including those initiated by proinflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). We have shown that systemic native immune system activation via i.p. injection of lipopolysaccharide (LPS) rapidly elevates CNS SERT activity and 5-HT clearance. Moreover, IL-1β can rapidly stimulate SERT activity in raphe nerve terminal preparations *ex vivo*, effects attenuated by pharmacological p38 MAPK inhibition. Because inflammatory cytokine signaling pathways are widely expressed, the role of p38 MAPK signaling in CNS 5-HT neurons in SERT regulation and attendant behavioral responses requires the use of conditional gene manipulation strategies. We engineered mice that afford elimination of p38α MAPK in 5-HT neurons (p38α5HT-) and used these animals and p38α5HT+ littermates to interrogate SERT regulation by peripheral LPS administration. p38α5HT- animals are viable and display no overt growth/behavior abnormalities and express normal levels of SERT protein and 5-HT transport activity. Consistent with pharmacological studies, however, midbrain synaptosomes from p38α5HT- animals fail to increase SERT activity in response to IL-1β application. Although LPS-treated p38α5HT- animals display normal elevations in central and peripheral inflammatory cytokines and plasma corticosterone, they fail to demonstrate elevations in midbrain SERT activity, and they lack typical depressive or anxiety-like behaviors characteristic of acute serotonergic manipulations. Our studies provide evidence for a critical role of 5-HT neuron p38α signaling in the translation of immune activation to SERT regulation and changes in behavior.

Disclosures: **N.L. Baganz:** None. **K.L. Lindler:** None. **C.B. Zhu:** None. **J.T. Smith:** None. **M.J. Robson:** None. **H. Iwamoto:** None. **E. Deneris:** None. **W.A. Hewlett:** None. **R.D. Blakely:** None.

Poster

811. Neuroimmunology: Behavioral Effects

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Topic: E.02. Neuroimmunology

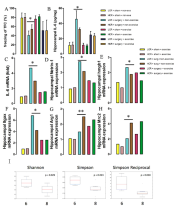
Support: NIH Grant 1R01GM104194-01

Departmental funding from UCSF

Title: Exercise improves postoperative cognitive decline in rats with metabolic syndrome by rectifying inflammation resolution and the microbiome

Authors: *X. FENG[1], S. VACAS[2], L. KOCH[3], S. BRITTON[3], M. MAZE[2];
[1]Anesthesia and Perioperative Care, [2]Anesthesia and Perioperative care, Univ. of California, San Francisco, San Francisco, CA; [3]Anesthesiol., Univ. of Michigan, Ann Arbor, MI

Abstract: Previously, we demonstrated that neuroinflammation induced by surgery causes cognitive decline (1,2). In a rat model of Metabolic Syndrome (MetaS), we have identified deficiencies in the resolution of inflammation following aseptic trauma (3,4). Here, we report on the role of exercise on acute postoperative memory decline in MetaS. Male low capacity runner (LCR) and high capacity runner (HCR) rats (4 months) were exercised 5 days/week for 6 weeks immediately prior to surgery. Following exercise, rats were trained in the trace-fear conditioning (TFC) paradigm 30 min before surgery. On day 3 after surgery, the rats were tested for freezing behavior; hippocampi were harvested for protein level of IL-6 and mRNA level of Il-6, Netrin-1, Hmgb-1, markers for pro-resolving macrophages (Arg1, Mrc2, Pparg, and Chi3l3) and pro-inflammatory macrophages (Nos2, Ccl2, Tnfa, and Itgax); stools were collected 1 day before and 3 days after surgery for 16s RNA sequencing of microbiome. LCR rats had less contextual freezing behavior than HCRs; however, exercise eliminated this difference. Hippocampal neuroinflammation was significantly activated in LCR+non-exe+surgery group than in HCR+non-exe+surgery; again, these differences were rectified by exercise. Furthermore, exercising the LCR rats rectifies their abnormal microbiome which becomes indistinguishable from the un-exercised HCR rats after. Pre-operative exercise may reverse the postoperative behavioral phenotype and normalize dysregulated inflammation-resolution. A: Freezing time in rats after exercise, TFC and tibia fracture. B - H: Hippocampal IL-6 protein level, IL-6, Netrin-1, Hmgb1, Itgax, Arg1, and Mrc2 mRNA level in rats after exercise, TFC and tibia fracture.*P<0.05, and **P < 0.01. N=6. I. Box plots summarizes the Shannon, Simpson, and Simpson Reciprocal diversity measures for microbiome. 1. Cibelli M, et al. Ann Neurol. 2010;68:360-8. 2. Terrando N, et al. Ann Neurol. 2011;70:986-95. 3. Feng X, et al. Anesthesiology. 2013;118:1098-105. 4. Su X, et al. Mol Med. 2013;18:1481-90



Disclosures: **X. Feng:** None. **S. Vacas:** None. **L. Koch:** None. **S. Britton:** None. **M. Maze:** None.

Poster

811. Neuroimmunology: Behavioral Effects

Location: Hall A

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Support: NIH grant AA022048

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NIGMS grant GM000678

Title: Basolateral amygdala astrocyte activation via DREADDs modulates ethanol consumption

Authors: *S. A. MARSHALL[1], T. E. THIELE[2], D. T. LYSLE[2];
[2]Dept. of Psychology and Neurosci., [1]Univ. of North Carolina, Chapel Hill, NC

Abstract: The role of the astrocytes in alcohol abuse has generally focused on neuroinflammation and its contributions to neurodegeneration, but astrocytes also play an integral role in modulating neuronal functions. Recent evidence indicates that astrocyte activation within the nucleus accumbens decreases the motivation to self-administer ethanol in dependent animals, but the actions of astrocytes in other regions and in non-dependent animals remains elusive. This study examines astrocyte activation within the basolateral amygdala (BlA) using the "drinking-in-the-dark" (DID) paradigm. The DID model is uniquely suited to study binge-like alcohol intake in non-dependent rodents. Male C57BL/6J mice were bilaterally infused with AAV8-GFAP-hM3D(Gq) or control virus within the BlA. This virus induces expression of Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) selectively on astrocytes. DID cycles consisted of three days of two hour access to 20% ethanol or 3% sucrose and a fourth day, or test day, where mice were given four hour access to ethanol or sucrose. Mice underwent four 4-day DID cycles. On the first two test days, ethanol consumption was measured after clozapine-N-oxide (CNO) administration. CNO specifically binds to and activates the Gq-DREADD construct. A two-way (virus x test day) RM ANOVA run on ethanol intake data indicated a main effect of viral treatment [$F(1,17)=12.01$, $p=0.003$] but no interaction or effect test day. To determine if the virus had an independent effect, mice received vehicle injections prior to ethanol solution access on the third test day and in this case

there were no significant differences between virus groups. Finally, on the fourth cycle test day, mice were given access to sucrose after CNO administration and results showed no virus group differences in sucrose drinking. Mice were also subjected to an open-field test after CNO administration to determine if astrocyte activation via Gq DREADDs altered locomotor activity or anxiety. T-tests indicated no significant differences between animals with the Gq DREADD and control viruses in total distance traveled, time spent in the center, or distance traveled in the center. Together these data suggest that activation of astrocytes within the BlA specifically reduces binge-like ethanol drinking. The mechanisms by which astrocyte activation modulates ethanol consumption are still elusive. Future studies should determine subsequent signaling cascades following activation of astrocytes that leads to reduced drinking. (Supported by NIH grants AA022048, AA013573, AA015148, AA011605 & NIGMS GM000678).

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Poster

811. Neuroimmunology: Behavioral Effects

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Topic: E.02. Neuroimmunology

Support: NIH Research Scientist Career Development Award (K01DK100616)

Medical College of Georgia Medical Scholars Program

Title: Pharmacological reinstatement of blood-brain barrier integrity prevents brain inflammation, synaptic dysfunction, and memory impairment in obese mice

Authors: ***S. HAO**[1], A. DEY[1], A. M. STRANAHAN[2];
[1]Med. Col. of Georgia, Georgia Regents Univer, Augusta, GA; [2]Neurosci. and Regenerative Med., Med. Col. of Georgia, Georgia Regents Univ., Augusta, GA

Abstract: Microglia form the predominant immune cell population in the brain and are protected from the systemic milieu by the blood-brain barrier (BBB). However, BBB permeability increases in certain pathologies, including obesity, which reduces expression of tight junction proteins that mediate adhesion between endothelial cells. While several reports have described correlations between BBB breakdown and cognitive impairment in obesity, the question of whether BBB breakdown causes obesity-induced memory deficits has never been addressed. Activation of protein kinase Cβ (PKCβ) causes BBB breakdown in models of infectious disease,

and we used the PKCβ antagonist LY-317615 to prevent BBB leakiness in mice with obesity due to consumption of a high-fat diet (HFD). After validating the reinstatement of BBB integrity in HFD mice treated with LY-317615, we examined hippocampal synaptic plasticity and performance in tests of hippocampus-dependent memory. Vehicle-treated HFD mice had reduced long-term potentiation (LTP) at medial perforant path synapses on dentate granule neurons relative to vehicle-treated mice maintained on a low-fat diet (LFD). Treatment with LY-317615 normalized LTP and prevented obesity-induced reductions in dendritic spine density and synaptic marker expression. Reinstatement of synaptic structure and function in HFD mice treated with LY-317615 was accompanied by normalization of spatial and object recognition memory. These parallel lines of evidence implicate BBB breakdown in microglial activation and deficits in hippocampal plasticity, but do not address whether direct interactions between microglia and neurons contribute to these effects. To address this possibility, we performed immunolabeling for IBA1 and PSD95, which revealed that vehicle-treated HFD mice had significantly greater overlap, even after correcting for increased coverage by IBA1-labeled processes. HFD mice treated with LY-317615 had very little colocalization between IBA1 and PSD95, suggesting that microglial phagocytosis of synapses might increase due to BBB breakdown in obesity. Because obesity is accompanied by peripheral inflammation, additional work will be necessary to determine the peripheral signal(s) that drive microglial activation, and identify the mechanisms that promote microglial internalization of hippocampal synapses.

Disclosures: **S. Hao:** None. **A. Dey:** None. **A.M. Stranahan:** None.

Poster

811. Neuroimmunology: Behavioral Effects

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Topic: E.02. Neuroimmunology

Support: NIH RO1NS073939

NIH RO1 NS074999

STARs award from University of Texas Systems

Title: T lymphocytes promote recovery from inflammation-induced comorbid pain and depression

Authors: *G. O. LAUMET, K. N. KRUKOWSKI, A. K. WALKER, R. DANTZER, C. J. J. HEIJNEN, A. KAVELAARS;
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Abstract: Chronic pain and depression are two of the most disabling and costly disorders in the USA and they frequently occur together. Increased prevalence of comorbid chronic pain and depression occurs in disease with a chronic inflammatory component such as cancer, diabetes and rheumatoid arthritis. Recent findings indicate that shared neuroimmune pathways underlie comorbid chronic pain and depressive behaviors in the context of peripheral inflammation. The contribution of innate immune cells to the onset of inflammation-induced pain and depressive disorders has been extensively studied, while the adaptive immune system has been under-studied. In addition, little is known about the neuroimmune mechanisms underlying the resolution of these comorbid symptoms. Interestingly, specific T lymphocyte populations may promote resolution of nerve injury-induced pain and a switch in T lymphocyte population profile has been reported in chronic pain patients. Given the high comorbidity of chronic pain and depression, we hypothesized that T lymphocytes are necessary to promote recovery from acute pain and depression induced by peripheral inflammation. Our preliminary data obtained in an animal model show that CD8+ T lymphocytes are necessary for resolution of chemotherapy-induced peripheral neuropathy. To determine the contribution of T lymphocytes in recovery from inflammation-induced pain and depression, we induced mechanical allodynia and depressive-like behavior by injecting 0.83 mg/kg lipopolysaccharide (LPS) i.p. in 9-week old C57Bl/6 (WT) mice and mice deficient in mature T and B lymphocytes (Rag1-/- mice). In Rag1-/- mice LPS-induced mechanical allodynia and depressive-like behaviors measured by increased immobility time in forced swim test were prolonged in comparison to wild-type C57Bl/6 mice. These differences were abrogated by reconstitution of Rag1-/- mice with CD3+ T lymphocytes from wild-type naive mice 7 days before LPS treatment. Interestingly, the involvement of T lymphocytes in recovery from LPS-induced comorbid depression and pain was specific since T lymphocytes did not contribute to recovery from LPS-induced sickness behaviors. These findings indicate that CD3+ T lymphocytes are important for endogenous resolution of acute inflammatory pain and depression and dysregulation of this endogenous recovery mechanism might be responsible for the transition of acute to chronic pain and depression.

Disclosures: G.O. Laumet: None. **K.N. Krukowski:** None. **A.K. Walker:** None. **R. Dantzer:** None. **C.J.J. Heijnen:** None. **A. Kavelaars:** None.

Poster

811. Neuroimmunology: Behavioral Effects

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Program#/Poster#: 811.17/X24

Topic: E.02. Neuroimmunology

Support: NINDS NS64571

Title: The CCL2:CCR2 axis controls infiltration of inflammatory monocytes into the brain during acute picornavirus infection

Authors: *R. G. LAFRANCE-COREY, C. HOWE;
Neurol., Mayo Clin., Rochester, MN

Abstract: Immune control of acute viral infection in the CNS requires a careful balance between efficient clearance of the virus and maintenance of neurologic function. We have observed hippocampal injury that compromises cognitive function and induces seizures following acute infection of C57BL/6 mice with the Theiler's murine encephalomyelitis virus. Injury is independent of direct neuronal infection with the virus and precedes the onset of an adaptive immune response, leading us to hypothesize that an early innate immune response causes the damage. Flow cytometric analysis of brain-infiltrating leukocytes indicated that mice experiencing hippocampal injury mount a robust inflammatory monocyte and neutrophil response in the brain within hours of infection. Microarray analysis, RTPCR, and ELISA revealed a robust pattern of chemokines and cytokines expressed in the brain and present in the serum within 3 hours of infection, including high levels of CCL2, CXCL1, and CXCL2. Genetic deletion of the chemokine receptor CCR2 abrogated infiltration of inflammatory monocytes into the brain, increased neutrophil infiltration, protected the hippocampus, preserved cognitive function, and reduced seizure activity, indicating a central role for the CCL2:CCR2 axis in the recruitment of inflammatory monocytes to the brain. Genetic deletion of CXCR2 blocked neutrophil infiltration but did not protect the brain or prevent seizures. We conclude that hippocampal injury and seizures during acute picornavirus infection are the result of bystander pathology triggered by infiltration of inflammatory monocytes in response to production of CCL2 in the brain.

Disclosures: R.G. Lafrance-Corey: None. **C. Howe:** None.

Poster

811. Neuroimmunology: Behavioral Effects

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 811.18/X25

Topic: E.02. Neuroimmunology

Support: NSERC

Title: Effects of neonatal infection on adolescent and adult anxiety in male and female rats and the development of 'anticipatory nausea'

Authors: *J. M. WARD[1], C. TENK[2], M. KAVALIERS[1], K.-P. OSSENKOPP[1];
[1]Univ. of Western Ontario, London, ON, Canada; [2]Brescia Univ. Col., London, ON, Canada

Abstract: Anticipatory nausea (AN) is a common symptom resulting from chemotherapy and other drug treatments. This form of nausea is a conditioned response where the illness resulting from the chemotherapeutic is paired with the environmental context of the hospital. On subsequent exposures to the environmental context, patients will experience nausea despite being in a drug-free state. There is mounting evidence in human populations that anxiety is a strong predictor in the development of anticipatory nausea. Rats are a non-emetic species lacking musculature and brainstem pathways to elicit an emetic response. Investigations of disgust in rats have shown that a behavioural response, known as gaping, is a strong index of anticipatory nausea-related behaviour. The present study is examining the effect of anxiety on AN. Prior research has suggested that this dual neonatal exposure to LPS in the neonatal stage is capable of causing anxiety-like behaviour in adulthood. Neonatal rats were injected with either lipopolysaccharide (LPS; 15 μg/kg or 50 μg/kg) or 0.9% isotonic saline on postnatal days (PND) 3 and 5. Anxiety-like behaviour is being assessed in adolescent rats (PND 42) and adulthood (PND 85) using the light-dark test. Adolescent male rats treated with 15 μg/kg of LPS showed significantly higher anxiety-like behaviour compared to male controls by spending more time in the dark chamber, $p < 0.05$. A significant drug by sex interaction was also found, $p < 0.05$. Female rats showed no significant effect. Anxiety-like behaviour will be reassessed on PND 80. In adulthood (PND90), anticipatory nausea-related behaviour in the rat will be examined by quantifying the gape response to an environmental context in a drug-free state after the context has been paired with the toxicosis resulting from lithium chloride treatment (64 mg/kg). These findings suggest that a neonatal LPS dose of 15 μg/kg is capable of eliciting anxiety-like behaviour in male adolescent rats assessed with the light-dark test and this provides a basis for examining the role of anxiety in the expression of anticipatory nausea.

Disclosures: J.M. Ward: None. **C. Tenk:** None. **M. Kavaliers:** None. **K. Ossenkopp:** None.

Poster

811. Neuroimmunology: Behavioral Effects

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Topic: E.02. Neuroimmunology

Support: DA 034721

T32 DA 07244

Title: DREADD activation of hippocampal astrocytes influences contextual fear conditioning

Authors: *M. E. JONES, D. BARRUS, C. L. LEBONVILLE, L. B. COOPER, D. T. LYSLE; Psychology and Neurosci., Univ. of North Carolina At Chapel Hill, Chapel Hill, NC

Abstract: Neuroimmune signaling is important in learning and memory processes. For example, our laboratory reported that stress induces a time dependent increase in hippocampal interleukin-1β (IL-1β) and that a central infusion of interleukin-1 receptor antagonist is sufficient to prevent stress-enhanced fear learning. Here, we tested whether activating hippocampal astrocytes altered contextual fear conditioning by employing Gq-coupled Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) under an astrocyte-specific promotor. Rats were infused with rAAV5/GFAP-HA-hm3D-IRES-mCitrine bilaterally into the dorsal hippocampus such that peripheral administration of Clozapine-N-Oxide (CNO) would activate Gq signaling selectively in hippocampal astrocytes. All animals were assigned to a foot shock treatment (foot shock or no foot shock) and a CNO treatment (CNO or vehicle). In Experiment 1, animals received three injections of either CNO (3 mg/kg, i.p.) or saline vehicle at 6, 4, and 2h prior to foot shock fear conditioning. For fear conditioning, animals were subjected to 5 2mA scrambled foot shocks on a 30s variable interval schedule in a distinct context. Control animals received the same treatment with no foot shocks. Twenty-four hours later, animals were placed back into the context and freezing behavior was analyzed. We found that 6h of astrocyte activation significantly enhanced fear learning as rats that received CNO followed by foot shock exhibited more freezing than rats that received vehicle followed by foot shock, $p < 0.02$. In Experiment 2, animals were subjected to the same foot shock fear conditioning paradigm as in Experiment, but received one injection of either CNO (3 mg/kg, i.p.) or saline vehicle immediately following conditioning. Animals were placed back into the conditioning context 24 hours later and freezing behavior was analyzed. Strikingly, astrocyte activation immediately following fear conditioning significantly attenuated fear learning as rats that received foot shock followed by CNO exhibited significantly less freezing than rats that received foot shock followed by vehicle, $p < 0.04$. Collectively, these findings indicate that hippocampal glial cell activation prior to stress induces a hypersensitivity to fear learning, but glial cell activation following stress interrupts fear memory consolidation. Future studies will explore the downstream mechanism through which Gq signaling alters fear learning and test whether Gq signaling directly induces neuroinflammatory signaling through the release of cytokines such as IL-1β.

Disclosures: **M.E. Jones:** None. **D. Barrus:** None. **C.L. Lebonville:** None. **L.B. Cooper:** None. **D.T. Lysle:** None.

Poster

811. Neuroimmunology: Behavioral Effects

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Topic: E.02. Neuroimmunology

Support: NIH R21MH101663

UDRF grant

COBRE 1P20GM103653-01A1

Title: Consequences of neonatal infection on immune function and spatial learning in juvenile male and female rats

Authors: ***B. OSBORNE**, J. CAULFIELD, J. SCHWARZ;
Dept. of Psychological and Brain Sci., Univ. of Delaware, Newark, DE

Abstract: Many developmental and psychiatric disorders exhibit strong sex differences with developmental disorders being strongly male biased. Many of these disorders have been linked to early-life immune activation; however, it has never been examined how sex impacts neonatal immune activation and how these factors may contribute to the onset of learning disorders during development. Microglia are the resident immune cells of the brain and respond to infections with rapid increases in cytokine release. Male rats have significantly more microglia in the hippocampus and amygdala compared to female rats on postnatal (P) day 4, thus, this time may represent a period in early development when males are more susceptible to infection than females. To address this hypothesis, we examined proinflammatory cytokine responses to infection at P4 in males and females 8 and 24 hours following a low dose of Escherichia coli (E.coli). Contrary to our predictions, males and females showed similar neuroimmune responses at P4 in the hippocampus, cerebellum, amygdala, and prefrontal cortex with neonatally infected animals showing exaggerated cytokine levels compared to saline controls (p's < .05); however; in the periphery (spleen) males showed significantly greater levels of IL-1ß and TNF-α 8 hours following neonatal infection compared to females (p's < .05). Next, we examined the long-term consequences of neonatal immune activation on subsequent immune activation in juvenile males and females by measuring cytokine responses to a second immune challenge of low-dose

lipopolysaccharide (LPS; 25µg/ml) at P24 either alone or following neonatal infection. We found that neonatally-infected males and females have significantly elevated levels of IL-1ß in the hippocampus and prefrontal cortex (PFC) at baseline and following a second immune challenge (p's < .05). To examine whether neonatal infection would result in developmental delays in learning in juvenile rats alone or in the presence of a second immune challenge, we tested juvenile rats at the onset of spatial learning using the Context Pre-exposure Facilitation Effect (CPFE) paradigm. Contrary to our predictions, we found that in the presence of a second immune challenge males and females that were neonatally infected showed enhanced learning relative to all controls ($p < .05$). These data suggest that neonatal infection enhances learning in the presence of a second immune challenge in male and female juvenile rats (at P24) and that increased IL-1ß levels in the brain may be a mechanism by which enhanced learning is occurring.

Disclosures: **B. Osborne:** None. **J. Caulfield:** None. **J. Schwarz:** None.

Poster

811. Neuroimmunology: Behavioral Effects

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Topic: E.02. Neuroimmunology

Support: CIHR

Title: A role for the LRRK2 G2019S mutation as a mediator of chronic inflammation in an immunological model of Parkinson's disease

Authors: *Z. DWYER, C. RUDYK, S. BELLEVUE, S. HAYLEY;
Neurosci., Carleton Univ., Ottawa, ON, Canada

Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. PD affects approximately 1% of the population over the age of 60 and results from the loss of dopamine producing neurons in the substantia nigra. PD has traditionally been characterized by a set of cardinal motor symptoms including bradykinesia, trembling and altered gait, however, recent work has highlighted several non-motor symptoms and co-morbidities. Importantly many of these have been linked to inflammatory processes and indeed several researchers have demonstrated that neurons in the substantia nigra are predisposed to cell death following inflammation. Leucine-Rich-Repeat Kinase 2 is a gene with unknown function which has been linked to both inflammation and PD. The Gly-2019S-Ser (G2019S) mutation

alone accounts for up to 10% of familian and 1.5% of sporadic PD cases. In our present study we sought to elucidate the role of the LRRK2 G2019S mutation as a potential genetic vulnerability in an immunological model of PD. B6.Cg-Tg(Lrrk2*G2019S)2Yue/J heterozygous mice were bred in house and with wild type (WT) littermates underwent stereotaxic surgery at 12 weeks of age to infuse 2µLs of saline, 1µg/µL Lipopolysaccaride (LPS) or 5µg/µL LPS. Animals were behaviourally assessed at several timepoints for indices of motor and sickness behaviour including home-cage locomotion, rotarod and gait analysis. Animals were perfused 21 days after surgery and both brains and peripheral organs were collected. G2019S mice were found to have significantly altered gait from WT animals regardless of treatment. G2019S animals showed no difference in sickness observed post-surgery, however, they regained lost weight significantly slower than WT LPS treated animals. Analysis of peripheral organs, blood brain barrier permeability, microglial activation, and TH+ cell counts revealed further differences between animals. LRRK2, specifically the G2019S mutation, appears to mediate the transition from acute inflammation to chronic inflammation in response to a central immunological insult (LPS).

Disclosures: **Z. Dwyer:** None. **C. Rudyk:** None. **S. Bellevue:** None. **S. Hayley:** None.

Poster

811. Neuroimmunology: Behavioral Effects

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Topic: E.02. Neuroimmunology

Title: Microglial alterations within the postpartum brain

Authors: ***A. HAIM**[1], K. LENZ[2], B. LEUNER[2];
[2]Psychology & Neurosci., [1]The Ohio State Univ., Columbus, OH

Abstract: The postpartum brain is remarkably plastic. In numerous brain regions, motherhood is associated with alterations in the production of new neurons as well as neuronal dendritic and synaptic remodeling. Postpartum modifications are not limited to neurons however, as astrocytic changes have also been documented. Possible postpartum-related alterations in microglia, the primary innate immune cells of the brain, haven't been examined although such a consequence is likely given the well-known peripheral immune changes that occur at this time, the role that microglia play in regulating neuronal plasticity, and the sensitivity of microglia to various hormones that are altered postpartum. To begin investigating this possibility, coronal brain sections from nulliparous female rats, pregnant rats on gestation day 20 and lactating rats on postpartum day 1 (early), postpartum day 8 (mid) and postpartum day 21 (PD21) were stained

for Iba1, a pan-microglial marker. Densitometry of Iba1 staining was performed in the hippocampus, medial prefrontal cortex, nucleus accumbens shell and basolateral amygdala. Our results show that compared to nulliparous females, Iba1 density was reduced during late gestation and early-mid postpartum in all regions examined. Furthermore, Iba1 density returned to nulliparous levels by the late postpartum period. These results are the first to reveal microglial alterations within the maternal brain and will lead to future studies investigating whether reduced Iba1 density reflects a reduction in microglia number and/or a change in microglial phenotype as well the underlying mechanism of these changes and their behavioral significance. While the involvement of microglia in developmental plasticity and pathological conditions is well known, microglial alterations during the postpartum period may provide a unique opportunity to gain a better understanding of how microglia modulate plasticity within the healthy adult brain.

Disclosures: **A. Haim:** None. **K. Lenz:** None. **B. Leuner:** None.

Poster

811. Neuroimmunology: Behavioral Effects

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 811.23/X30

Topic: E.02. Neuroimmunology

Support: R01-MH-093473

R01-MH093472

R01-AG033028

T32-DE014320

Title: Repeated social defeat stress induces neuroinflammation and impairs hippocampal neurogenesis that differentially regulate mood and cognition

Authors: *A. NIRAULA, D. MCKIM, A. TARR, J. SHERIDAN, J. GODBOUT;
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Abstract: Repeated social defeat (RSD) is a murine stressor that models several key physiological, immunological, and behavioral alterations observed in humans exposed to psychosocial stress. RSD induces prolonged anxiety-like behavior associated with myeloid cell trafficking into the brain, including the hippocampus - a key area involved in neuroplasticity, behavior, and cognition. Therefore, the goal of this study was to investigate if the stress-induced

monocyte trafficking affected hippocampal neurogenesis and cognitive function. Here, we show that RSD increased inflammatory mediators (IL1b, TNFa and IL-6) in the hippocampus, and enhanced microglia activation and monocyte trafficking (CD45hi) specifically in the caudal hippocampus. RSD also impaired spatial memory recall in the Barnes maze independent of anxiety-like behavior. RSD did not affect the number of proliferating neural progenitor cells and developing neurons when examined 14 hours post-RSD. However, there was a significant reduction in the number of young neurons and mature neurons when examined 10 days and 28 days post-RSD respectively. Consistent with region-specific neuroinflammation, reduction in the number of mature neurons was greater in the caudal hippocampus of the RSD mice compared to controls. The RSD-induced spatial deficits, which are rostral hippocampus-mediated, were resolved by 28 days. Social avoidance which is caudal hippocampus-mediated still persisted 28 days after stress. Thus, stress-induced neuroinflammation is associated with reduced neuroplasticity, and the stress-induced affective and cognitive deficits are differentially associated with hippocampal neurogenesis.

Disclosures: **A. Niraula:** None. **D. McKim:** None. **A. Tarr:** None. **J. Sheridan:** None. **J. Godbout:** None.

Poster

811. Neuroimmunology: Behavioral Effects

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 811.24/X31

Topic: E.02. Neuroimmunology

Support: Olle Engkvist Byggmästare Foundation

Berzelii Centre Stockholm Brain Institute

Strategic Research Program in Neuroscience

Knut and Alice Wallenberg Foundation

Title: Prenatal antibiotic exposure alters brain development and behavior: Implications for neurodevelopmental disorders

Authors: *T. B. ARENTSEN, H. RAITH, H. FORSSBERG, R. DIAZ HEIJTZ;
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Abstract: A growing number of studies have recently revealed that the indigenous gut microbiota has much wider effects on host physiology and development than originally believed, including the early-life programming of brain circuits involved in the control of emotions, motor activity, and cognitive functions. Therefore, perturbations of the gut microbiota, during key neurodevelopmental stages, may affect early life gut-microbiome brain interactions, altering brain development and behavior. In the present study, we examined the specific contribution of the maternal gut microbiota during pregnancy to brain development and behavior in the offspring. For this purpose, pregnant female C57BL/6N mice were exposed to a broad-spectrum antibiotic treatment in the drinking water during the entire pregnancy. Treatment was stopped immediately after delivery. To determine potential long-term behavioral changes in the offspring, we subjected prenatal-antibiotic treated male and female mice to a battery of tests for motor activity, anxiety-like behavior, sociability and preference for social novelty during the prepubertal period (i.e., P22-25). In the open-field test, we found significant sex-dependent changes in the spontaneous motor activity of juvenile mice exposed to prenatal antibiotic treatment. Prenatal antibiotic-treated males travelled a greater total distance during the initial 15 min of testing (i.e., novelty phase), but not habituation, testing periods than did controls. In contrast, the same treatment in females led to increased levels of both locomotion and rearing activity during the habituation, but not the initial testing, periods, indicating that their hyperactivity was not triggered by novelty. Anxiety-like behavior was not altered by prenatal antibiotic exposure. In the three-cambered social approach test, prenatal-antibiotic treated male mice displayed a significant increase in sociability, as indicated by increased time spent in a chamber containing a stimulus mouse versus the alternative empty chamber. These mice also showed increased preference for social novelty. Adult males exposed to antibiotics during prenatal life showed similar increased levels of social behavior. Interestingly, social behavior was not affected in prenatal-antibiotic treated female mice. Our results indicate that perturbations of the maternal gut microbiota during pregnancy may have life-long lasting effects on brain development and behavior in the offspring, and that these effects are sex-dependent.

Disclosures: **T.B. Arentsen:** None. **H. Raith:** None. **H. Forssberg:** None. **R. Diaz Heijtz:** None.

Poster

811. Neuroimmunology: Behavioral Effects

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 811.25/X32

Topic: E.02. Neuroimmunology

Support: Division of Intramural Research, NINR, NIH

Title: Follow the TRAIL: understanding the etiology of persistent fatigue and cognitive impairment following radiation therapy

Authors: L. FENG[1], *K. A. MAGUIRE-ZEISS[2], L. N. SALIGAN[1];
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Abstract: Fatigue is one of the most debilitating side effects of cancer and cancer therapy, and it persists long after treatment completion. In this study, we aimed to investigate changes in immunological markers and cognitive functions in fatigued men receiving external beam radiation therapy for non-metastatic prostate cancer. A sample of 34 men with prostate cancer scheduled to receive radiation therapy were followed at baseline (prior to treatment initiation) and one year after treatment completion. Demographic and clinical data were obtained by chart review. The Functional Assessment of Cancer Therapy-Fatigue (FACT-F) was administered to measure fatigue levels. The Computer Assessment of Mild Cognitive Impairment (CAMCI®), a computerized screening tool was administered at each time point to evaluate cognitive decline. Blood was drawn at baseline and one year after completion of radiation therapy; plasma cytokine levels were determined using the Bio-Rad Bio-Plex Cytokine Assay Kits. Gene expression profiles were determined using microarray analysis and analyzed using Partek Genomics Suite 6.6 as well as Ingenuity Pathway Analysis. At one year after EBRT completion, 34% of subjects continued to experience persistent fatigue, defined as a decline in FACT-F scores of 3 points or greater. Fatigued subjects also exhibited signs of mild cognitive impairment as measured by CAMCI. Microarray analysis of blood samples collected one year following radiation therapy revealed 44 genes that were differentially expressed between fatigued and non-fatigued subjects. The main disease networks identified by pathway analysis are related to cancer pathophysiology. Compared to non-fatigued subjects, there was an increase in expression levels of the decoy receptor TRAIL-R3 in the fatigued group. Interestingly, the ligand of this receptor, TRAIL, is also significantly upregulated in fatigued subjects. Evidence of the involvement of cancer disease networks as well as the concomitant upregulation of TRAIL and its decoy receptor suggest that fatigue and cognitive impairment may be more than distressing side effects of cancer treatment. Instead, these symptoms may serve as behavioral indicators of the underlying disease status in cancer patients.

Disclosures: L. Feng: None. **K.A. Maguire-Zeiss:** None. **L.N. Saligan:** None.

Poster

811. Neuroimmunology: Behavioral Effects

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 811.26/X33

Topic: E.02. Neuroimmunology

Support: NIH MH087978

Title: A clinically relevant model of prenatal inflammation (intrauterine lipopolysaccharide) results in offspring hyperactivity

Authors: N. GRISSOM[1], S. MCKEE[1], *T. M. REYES[2];
[1]UNIV OF PENNSYLVANIA, PHILADELPHIA, PA; [2]Pharmacol., Univ. Pennsylvania, Sch. of Med., Philadelphia, PA

Abstract: Maternal infection during pregnancy is common and can cause adverse neurodevelopmental outcomes. While systemic administration of bacterial or viral mimetics are widely used models of prenatal inflammation, an alternative approach is local inflammation of the uterus, which models chorioamnionitis (inflammation of the fetal membranes). Importantly, this mimics the most common human clinical scenario by which a fetus is exposed to prenatal inflammation. Using CD-1 mice, local inflammation was induced via intrauterine lipopolysaccharide (LPS) infusion at E15 (term = E19). Behavioral, molecular and immune endpoints were evaluated in adult offspring. Males and females demonstrated hyperactivity, as well as an overall decrease in anxiety-like behavior (open field, elevated zero, light-dark box). Operant testing was initiated to examine executive function, however all mice (regardless of prenatal condition) failed to reach criterion performance, which may be due to reduced visual acuity in the albino CD1 strain. Prenatal LPS exposure increased the number of microglia, quantified by flow cytometric analysis of the whole brain. Expression of 30 genes related to immune, epigenetic and neurotransmitter function was measured, both at baseline and in response to an acute immune challenge, and these analyses are ongoing. These data indicate that local inflammation of the uterus, in the absence of a maternal plasma cytokine response, affects offspring brain development, and support additional work in this translationally relevant model of prenatal inflammation.

Disclosures: **N. Grissom:** None. **S. McKee:** None. **T.M. Reyes:** None.

Poster

812. Stress and Cognitive Function

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 812.01/X34

Topic: E.05. Stress and the Brain

Support: Andrews University Faculty Research Grant 201166

Title: Fit but Frazzled? Comparing the effects of chronic stress and fitness on college freshmen

Authors: M. KIM[1], R. R. CLOUSE[1], L. A. MUASAU[1], K. G. BAILEY[2], *P. S. LITVAK[1]; [1]Biol., [2]Psychology, Andrews Univ., Berrien Springs, MI

Abstract: College freshmen face several unique stressors, including adjusting to a new living and academic environment, and dealing with mounting financial obligations. Chronic stress leads to structural changes in the prefrontal cortex and hippocampus that cause cognitive impairment. But interestingly, exercise is a physical stressor that facilitates function in these brain areas. The goals of the current study were to: 1) compare the effects of physical fitness vs. stress on memory performance in college freshmen (n=22), and 2) compare the effects of fitness vs. stress on the students' acute stress response. Preliminary data indicated that higher fitness levels may have been associated with improved hippocampus-dependent memory scores ($p = 0.08$, Cohen's $d=0.7$) , but not prefrontal cortex memory. Higher fit students had an increased salivary cortisol response but decreased blood pressure response to a mild, cognitive stressor ($p < 0.05$). Students with higher self-reports of stress performed significantly worse on the prefrontal cortex-based task ($p < 0.05$) and showed a statistical trend for impairment on the hippocampus-based task ($p = 0.06$). Higher stress levels resulted in a significant decrease in salivary cortisol and increase in blood pressure to a mild, cognitive stressor ($p < 0.05$).

Disclosures: M. Kim: None. **R.R. Clouse:** None. **L.A. Muasau:** None. **K.G. Bailey:** None. **P.S. Litvak:** None.

Poster

812. Stress and Cognitive Function

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 812.02/X35

Topic: E.05. Stress and the Brain

Title: Reactivation of a fear memory prior to learning sex-dependently influences long-term memory

Authors: *A. M. DAILEY[1], C. E. CADLE[1], D. M. PETERS[1], A. E. KALCHIK[1], R. L. AUFDENKAMPE[1], C. M. BROWN[1], A. R. SCHARF[1], M. B. EARLEY[1], C. L. KNIPPEN[1], H. E. NAGLE[1], B. R. RORABAUGH[2], P. R. ZOLADZ[1];
[1]Psychology, Sociology, & Criminal Justice, [2]Pharmaceut. & Biomed. Sci., Ohio Northern Univ., Ada, OH

Abstract: Despite having powerful memories of their trauma, individuals with post-traumatic stress disorder (PTSD) display a paradoxical deficit for learning new information. Investigators have speculated that this impairment results from intrusive memories transiently interfering with the ability of PTSD patients to process new information. However, due to the ethical problem of provoking traumatic memories in PTSD patients, this hypothesis has gone unstudied in humans. Thus, the purpose of the present study was to examine the effects of fear memory reactivation on subsequent learning in humans, thereby providing a basic model of intrusive memory effects on cognitive processing. On Day 1, participants sat in a dark room and viewed a fear-inducing or control video in the presence of a non-related, but constant, background auditory stimulus (tone). The next day, participants returned to the laboratory and sat quietly in a dark room with the same background auditory stimulus for 3 min to reactivate the memory of the video from the previous day. Immediately following reactivation, participants viewed 30 images varying in emotional valence. Participants underwent free recall testing immediately after learning. Twenty-four hours later, participants returned to the laboratory and completed free recall and recognition assessments. Results revealed that reactivation of the fear video memory led to impaired 24-hr recall in males, but not females. Independent of sex, there was a significant negative correlation between systolic blood pressure response to fear memory reactivation and emotional picture recall. Interestingly, in females, systolic blood pressure response to fear memory reactivation was positively correlated with negative picture recall. These findings reveal sex-dependent effects of fear memory reactivation on emotional memory and may provide insight into the mechanisms underlying intrusive memory-induced modulation of cognitive processing in people with PTSD.

Disclosures: **A.M. Dailey:** None. **C.E. Cadle:** None. **D.M. Peters:** None. **A.E. Kalchik:** None. **R.L. Aufdenkampe:** None. **C.M. Brown:** None. **A.R. Scharf:** None. **M.B. Earley:** None. **C.L. Knippen:** None. **H.E. Nagle:** None. **B.R. Rorabaugh:** None. **P.R. Zoladz:** None.

Poster

812. Stress and Cognitive Function

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 812.03/X36

Topic: F.02. Animal Cognition and Behavior

Support: VA Merit Review/Career Scientist Award

Title: Inhibitory avoidance, but not fear conditioning, impairs spatial memory retrieval: insight into how different forms of trauma memory processing affect new memory processing

Authors: C. R. PARK[1,2], P. R. ZOLADZ[3], *D. M. DIAMOND[1,2];
[1]Psychology, Univ. South Florida, Tampa, FL; [2]Res. and Develop., VA Hosp., Tampa, FL;
[3]Psychology, Sociology & Criminal Justice, Ohio Northern Univ., Ada, OH

Abstract: One of the hallmarks of post-traumatic stress disorder (PTSD) is the occurrence of recurrent, intrusive memories of the traumatic event. A consequence of repeated intrusive memory reactivation is that new memory processing can be impaired. Zoladz and Diamond (Neurosci. Biobehav Rev 2013) addressed this issue, suggesting that reactivation of trauma memories produces heightened anxiety, which interferes with hippocampal functioning during cognitive testing. We studied an analogous phenomenon in rats in which activation of a fear-provoking memory, up to one year after the original traumatic event, interfered with retrieval of a newly acquired spatial memory (Zoladz et al. Stress, 2010). That work showed that retrieval of the memory for shock inhibitory avoidance (IA) impaired the retrieval of the memory for the hidden platform location in a radial-arm water maze task (RAWM). In the current work we have extended this investigation to include two different fear-provoking tasks, classical fear conditioning (FC) and predator-based fear conditioning (PBFC), as the memory reactivation stimuli. We hypothesized that training or memory reactivation for FC and PBFC would impair retrieval of water maze spatial memory. Adult male rats were trained on IA, FC or PBFC tasks. One day later they were trained on a spatial memory task to locate a hidden escape platform in a radial-arm water maze. Memory for the platform location was tested 30 min later. Immediately before the spatial memory retrieval trial, the rats were re-exposed to the fear-provoking apparatus where they had been trained 24 hr previously. Other groups of rats were administered IA, FC or PBFC during the 30 min period between water maze learning and memory testing. Neither training nor retrieval of fear conditioning interfered with short-term (30 min) spatial memory. Re-exposure to the context associated with predator stress (PBFC) also did not interfere with spatial memory. Though all three tasks used an aversive stimulus to generate a fear-provoking memory, only IA training and memory testing impaired spatial memory. This finding suggests that differences in processing of the IA vs FC contingency, perhaps in terms of differences in cognitive resource allocation and the differential involvement of the prefrontal cortex in the two tasks, may explain why IA training is so intrusive. The intrusiveness of IA memory processing may provide a better model than FC for traumatic memory processing in PTSD.

Disclosures: C.R. Park: None. **P.R. Zoladz:** None. **D.M. Diamond:** None.

Poster

812. Stress and Cognitive Function

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 812.04/X37

Topic: E.05. Stress and the Brain

Support: NIH Grant MH053851

Title: Effects of chronic unpredictable stress and chronic intermittent cold stress on cognitive flexibility in female rats

Authors: *D. PAREDES, J. D. SILVA, D. A. MORILAK;
Pharmacol. and Ctr. for Biomed. Neurosci., Univ. of Texas Hlth. Sci. Ctr. San Anto, San Antonio, TX

Abstract: Susceptibility to stress-related neuropsychiatric disorders, such as depression, post-traumatic stress disorder and other anxiety disorders, is higher in women than in men. However, there is limited research on the mechanisms underlying these gender differences in animal models of such disorders. Chronic stress is a known risk factor for many of these neuropsychiatric disorders. They are often characterized by cognitive and emotional biases, such as perseverative thought and cognitive inflexibility, which can be promoted by stress. Our research in male rats has shown chronic stress to induce prefrontal cortical dysfunction and associated impairments in cognitive flexibility, including deficits in reversal learning and cognitive set-shifting. Specifically, chronic unpredictable stress (CUS) induced deficits in set-shifting, mediated in the ventral medial prefrontal cortex, whereas chronic intermittent cold (CIC) stress produced a selective deficit in reversal learning, mediated in the orbitofrontal cortex. However, these studies have all been conducted using male rats. It is unknown if chronic stress induces similar cognitive deficits and prefrontal cortical dysfunction in female rats. Thus, the purpose of this study was to examine the effects of CIC stress and CUS on cognitive flexibility in female rats using the attentional set-shifting test (AST). We hypothesized that female rats would exhibit deficits in cognitive flexibility after chronic stress similar to those seen in males. Adult female Sprague Dawley rats underwent 14 days of CIC (4°C, 6hr/day) or no stress, and were subsequently tested for reversal learning on the AST. Control rats were handled daily prior to testing. Another cohort of females received 14 days of CUS or control treatment and were tested on Day 15 for reversal learning and set-shifting on the AST. As predicted, CIC rats showed a deficit in reversal learning compared to controls ($p<0.01$). By contrast, no differences were observed in reversal learning or set-shifting between CUS and control female rats, contrary to previous results in males. However, because we had to modify several components of the CUS procedure to accommodate female subjects (for example, we had to eliminate the social defeat

stimulus, and replaced it instead with footshock), we cannot determine if the lack of effect was truly due to a gender difference in susceptibility to CUS, or if these modifications to the CUS procedure rendered it less stressful in females. In subsequent experiments, we will test the effect of antidepressant drugs, including SSRIs, on the deficit in reversal learning induced by CIC stress in females.

Disclosures: D. Paredes: None. **J.D. Silva:** None. **D.A. Morilak:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Lundbeck A/S. F. Consulting Fees (e.g., advisory boards); Lundbeck A/S.

Poster

812. Stress and Cognitive Function

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 812.05/X38

Topic: E.05. Stress and the Brain

Support: CONACYT 238313

IMSS 2011032

Title: Permanent effects of environmental noise on working memory and astrocyte proliferation in the medial preforntal cortex

Authors: *Y. RUVALCABA DELGADILLO[1], T. MORALES-SALCEDO[2], G. YAÑEZ-DELGADILLO[2], P. HERNÁNDEZ[2], G. CHIPRÉS-TINAJERO[2], R. RAMOS-ZÚÑIGA[2], A. FERIA-VELASCO[2], J. GARCÍA-ESTRADA[3], F. JAUREGUI-HUERTA[2], M. LUQUÍN[2]; [1]Neurosci., Univ. De Guadalajara, Guadalajara, Mexico; [2]Univ. de Guadalajara, Guadalajara, Mexico; [3]Inst. Mexicano del Seguro Social, Guadalajara, Mexico

Abstract: Aversive experiences during development can influences maturity process of the nervious and endocrine systems. Environmental exposure to aversive estimuli activate the stress response and thus the release of glucocorticoids (GLCs). GLCs are involved in multiple functions through their receptors distributed in Central Nervous Sistem (CNS) structures, including the medial prefrontal cortex (mPFC). mPFC regulates the activity of the stress response and is involved in cognitive functions such as working memory. Also this structure is vulnerable to early experiences because of its intense maturational activity in postnatal life.

Much of the cells in the CNS have receptors for GLCs and these hormons can be deletereous effects if they released in excess. These cells include astrocytes, which have a lot important fuctions, regulate neuronal micro environmental, possess transport systems for the neuro trans mitters and their precursors, regulate synapsis circuits and exert crucial neuro endocrine functions. Astrocytes also play a central rol in the defense against damage by modifying their pro liferative activity and morphology. We evaluated the long-term effects of noise by assessing both, astrocyte changes in medial prefrontal cortex (mPFC) and mPFC related alternation/discrimination tasks. METHODS: 21-day-old male Wistar rats were exposed to environmental noise (EN) in a 24-h fashion. We used for this purpose a standardized rats' audiogram-fitted adaptation of a human noisy environment. We measured corticosterone (CORT) serum levels at the end of the exposure and registered body weight gain during the first 2 weeks of the experiment. In order to assess non-auditory long-term effects of the early EN exposure, we assessed the rats' performance on T-Maze related PFC tasks and measuring the astrocyte numbers in the mPFC 10 months after the end of the exposure to EN. RESULTS: EN increased the levels of CORT of the rats exposed even after fifteen days of exposure and negatively affected the body weight gain. Accordingly, enduring effects of noise were also demonstrated on mPFC structure and function. The ability to solve alternation/discrimination tasks were reduced as well as the numbers of astroglial cells in the mPFC. CONCLUSION: Chronic EN produced stressing effects evidenced by the increased circulating levels of CORT. The exposure to this developmental stress model may have enduring effects as suggested by the decrease of the performance on T-Maze related mPFC tasks in the mPFC astrocityc population.

Disclosures: **Y. Ruvalcaba Delgadillo:** None. **T. Morales-Salcedo:** None. **G. Yañez-Delgadillo:** None. **P. Hernández:** None. **G. Chiprés-Tinajero:** None. **R. Ramos-Zúñiga:** None. **A. Feria-Velasco:** None. **J. García-Estrada:** None. **F. Jauregui-Huerta:** None. **M. Luquín:** None.

Poster

812. Stress and Cognitive Function

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 812.06/X39

Topic: E.05. Stress and the Brain

Support: NIH Grant DA07606

Title: Chronic stress, cognitive dysfunction and serotonin innervation to the medial prefrontal cortex from the dorsal raphe

Authors: *R. NATARAJAN, N. L. CHIAIA, N. A. NORTHROP, B. YAMAMOTO;
Dept. of Neurosciences, Univ. of Toledo, Toledo, OH

Abstract: Stress differentially activates specific subregions of the dorsal raphe (DRN) serotonergic (5HTergic) cells to affect 5HT release in forebrain targets such as the medial prefrontal cortex (mPFC). The mPFC mediates cognition and chronic exposure to stress is known to affect mPFC function. However, the mechanism underlying stress induced dysfunction of the mPFC is unknown. We tested the hypothesis that exposure to chronic unpredictable stress (CUS) decreases 5HT cells in the DRN leading to fewer 5HTergic innervation of the mPFC and resulting in persistent cognitive deficits. Adult male Sprague-Dawley rats underwent 21 days of CUS or daily handling (NoCUS). One week after the end of CUS, 5HT cells were counted in the ventromedial, dorsomedial, ventrolateral, and interfascicular (DRI) subregions of the DRN. Results show that CUS caused a 43.2 ± 8.9 % decrease in 5HT cells that is specific to the DRI subregion. Additionally, experiments were conducted to determine if corticosterone (CORT) played a role in CUS induced 5HT cell decreases in the DRI. Rats received 50 mg/kg metyrapone (Mety), a CORT synthesis inhibitor, or 10% EtOH vehicle (Veh), i.p., 15 min prior to each stressor. After CUS, a retrograde tracer TrueBlue was injected bilaterally into the mPFC to ascertain that CUS decreased DRI cells that innervate mPFC. Tracer positive soma were counted in the DRI one week after termination of CUS and results show that CUS caused a (CUS+Veh = 42.6 ± 7.6 %) loss of cells in the DRI that project to the mPFC and Mety pretreatment during CUS significantly blocked this effect (CUS+Mety = 80.9 ± 7.1 %). To assess CUS dependent deficits in cognitive function, 4 weeks after CUS, rats pretreated with Veh or Mety during CUS underwent Barnes maze testing. Results show no difference in the latency to acquire the task between CUS and NoCUS. However, the latency to recall the location of the goal box after a 2 day break from the maze was increased in the CUS+Veh group (NoCUS+Veh = 17.8 ± 2.6 s, CUS+Veh = 34.7 ± 3.9 s, $p < 0.05$). Additionally, the latency to find the goal box in a new location was significantly increased in the CUS+Veh group compared to NoCUS+Veh, and Mety pretreatment during CUS blocked this deficit in reversal learning (NoCUS+Veh = 22.5 ± 4.1s, CUS+Veh = 67.8 ± 14.7 s, CUS+Mety = 22.0 ± 4.2 s, $p < 0.05$), indicating that CUS causes long-term deficits in memory recall and perseveration, and that CORT mediates CUS induced deficits in behavioral flexibility. These results suggest that CUS induced loss of 5HT neurons of the DRI decreases 5HTergic innervation of the mPFC to cause lasting cognitive dysfunction. Future experiments will focus on the mechanism mediating these cognitive deficits.

Disclosures: R. Natarajan: None. **N.L. Chiaia:** None. **N.A. Northrop:** None. **B. Yamamoto:** None.

Poster

812. Stress and Cognitive Function

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 812.07/X40

Topic: F.02. Animal Cognition and Behavior

Title: A novel behavior of unconditioned fear: characterization and quantification of the K-turn

Authors: K. J. KUJAWA[1], *M. BABCOCK[2];
[1]Psychology, [2]Montana State Univ., Bozeman, MT

Abstract: A detailed behavioral analysis was conducted on mice tested in a traditional unconditioned olfactory fear paradigm. Previous studies have relied on proximity, freezing, or time spent exploring the fear scent. In the present series of studies, we documented several novel behaviors that may represent important responses to odors that are fearful to rodents. Mice in the present study were exposed to a cloth without predator odor for 5 min on four consecutive testing days. On the fifth day, mice were exposed to a cloth containing cat odor for 5 min. When exposed to the predator odor, mice displayed a behavior pattern that has not been previously reported in the literature. Specifically, mice responded by displaying a stretch-attend behavior and, upon returning to the original position, retreated from the odorant to the far side of the apparatus. The frequency of this behavior pattern was significantly higher relative to the previous trial when the predator odor was not present. For the purposes of distinguishing this behavior from the stretch-attend behavior, we term this behavioral sequence a K-turn. Our study characterizes the K-turn and its relationship with other behaviors traditionally measured in unconditioned fear paradigms. We have evaluated K-turns in animals tested during different periods of the light-dark cycle. The results of the present study offer additional behavioral measurements that may provide greater sensitivity in detecting fear-related responses. The addition of the K-turn behavioral sequence many represent a sensitive and valid marker of a fear response.

Disclosures: K.J. Kujawa: None. **M. Babcock:** None.

Poster

812. Stress and Cognitive Function

Location: Hall A

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Program#/Poster#: 812.08/X41

Topic: E.05. Stress and the Brain

Support: PAPIIT IN305715

PAPIME PE300715

Title: Long-term effects caused by the exposure to unpredictable chronic stress

Authors: *H. SANCHEZ-CASTILLO[1,2], P. TORRES-CARRILLO[1], B. ROJAS-LITA[1], C. MENDOZA-ROSALES[1], M. MIGLIARO[1], D. B. PAZ-TREJO[1,2], V. M. SOLIS[1], E. HONG[3]; [1]Univ. Nacional Autonoma De Mexico. Fac Psicologia, Mexico City, Mexico; [2]Sociedad Iberoamericana de Neurociencia Aplicada, Mexico City, Mexico; [3]Farmacologia, CINVESTAV, Mexico City, Mexico

Abstract: There is a current research interest that is focused on elucidating the effects of chronic stress on brain structures involved in the modulation of behavioral patterns, such as the prefrontal cortex (PFC). The functional impairment of the PFC that occurs during high levels of stress is significant for understanding the condition of mental health of patients with stress-related disorders. In addition, loss of self-control during exposure to stress can bring a large number of maladaptive behaviors, such as substance abuse. On the other hand, it has been described that intense stressful events (such as natural disasters, military combat, sexual abuse or domestic violence) can lead to Post-traumatic Stress Disorder (PTSD). However, not sufficient attention has been given to the long-term effect that exposure to chronic stress has on cognition after an interval of recovery. The objective of this research project was to evaluate the effect of chronic unpredictable stress in a Y-maze task, which served as a measuring tool for behavioral flexibility. Performance was compared among different rat strains: Wistar, Wistar Kyoto, and SHR. All experimental subjects were male and had an approximate age of four months at the beginning of the experiment. Animals were exposed to a Chronic Unpredictable Stress Battery (CUSB) for ten days. The behavioral assessments were performed before, immediately after (acute effects), and after a temporary recovery window of three months (persistent effects) after the CUSB exposure. Differential results were observed dependent to the rat strains. The rats belonging to the Wistar strain had an increase in the number of sessions required to satisfy the learning criteria, on the second evaluation that assessed acute effects compared to the first evaluation, meanwhile on the first evaluation and on the third evaluation we observed similar values for the number of errors and latency (both lower than those of the second evaluation). With the SHR strain, no distinguishable effects caused by the stress exposure were observed on all three evaluations. The rats belonging to the Wistar Kyoto strain showed a considerable increase in the number of errors and latency on the third evaluation, which suggests that this strain is susceptible to the long-term effects of stress even after the window of recovery. It is notable to mention that not all subjects from the SHR and Wistar Kyoto strains achieved the learning criteria in the first evaluation.

Disclosures: H. Sanchez-Castillo: None. **P. Torres-Carrillo:** None. **B. Rojas-Lita:** None. **C. Mendoza-Rosales:** None. **M. Migliaro:** None. **D.B. Paz-Trejo:** None. **V.M. Solis:** None. **E. Hong:** None.

Poster

812. Stress and Cognitive Function

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 812.09/X42

Topic: F.02. Animal Cognition and Behavior

Title: Acute restraint stress alters adult zebra finch song performance and neuronal morphology: Potential model for evaluation of neurobiological effects of developmental stress

Authors: *T. L. HOLLAND, K. SODERSTROM;
East Carolina Univ., Greenville, NC

Abstract: During a sensitive period of development, male zebra finches learn a complex song that is important to courtship. During early stages of vocal development they listen to and memorize an adult's song, forming a template. Later in development they gradually improve the song by practicing and using auditory feedback. In adulthood, the song has low variability and is stable over time. This process parallels language acquisition in humans. We are interested in the effect of psychological stress on vocal development in zebra finches. Currently, we have evaluated the effect of acute restraint stress on song performance and corresponding neuronal morphology in adult zebra finches. We hypothesized that stress would alter spectral and temporal features of the adult's song. Zebra finches (n = 4-5) were administered 30 minutes of restraint stress or 30 minutes of no stress, immediately followed by two hours of audio recording. A female audience bird was presented as a social stimulus to promote singing. Songs were compared to previously obtained baseline recordings in a paired design. Sound Analysis Pro software was used to analyze songs and export spectral and temporal data for each song syllable. Song syllables of the stress group had significantly higher pitch and longer duration when compared to baseline recordings (Wilcoxon signed-rank test, $p < 0.05$). The no stress group had no significant differences from baseline recordings. In a complimentary experiment, adults were administered acute restraint stress (n = 5), and following cessation of the stressor, brains were collected for Golgi-Cox staining in order to evaluate changes in dendritic spine density as a morphological measure of neuronal activity. In a premotor brain region for song production (HVC), no changes were observed. In NCM, a secondary auditory region, dendritic spine densities increased. Since no clear alteration within the motor circuit was observed, altered spectral and temporal features following restraint stress may be related to altered synaptic activity within the auditory system. The stress-altered song may be an adaptive response, possibly relevant to communicating anxiety. In the future, we will evaluate the effects of concurrent developmental stress and cannabinoid CB1 receptor agonist treatment on vocal

learning in order to learn more about the neurobiological consequences, and potential interaction of stress and drug abuse on developmental-dependent learning.

Disclosures: T.L. Holland: None. **K. Soderstrom:** None.

Poster

812. Stress and Cognitive Function

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 812.10/X43

Topic: E.05. Stress and the Brain

Support: FONDECYT Grant N° 1141276 to AD-S

FONDECYT 1130614 grants to MF

Title: Anti-stress effects and memory enhancer properties of n-3 PUFA in stressed rats

Authors: *A. DAGNINO-SUBIABRE[1], M. A. PÉREZ[2], V. PEÑALOZA-SANCHO[2], J. AHUMADA[3], M. FUENZALIDA[3];
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Abstract: While chronic stress induces dendritic atrophy in the hippocampus and impairs learning and memory, supplementation with n-3 Polyunsaturated fatty acid (PUFA) is known to improves learning and memory of unstressed rats. Whether n-3 PUFA supplementation could improve dendritic morphology and memory of stressed rats, as well as decrease the major stress markers, remain unknown. Male Sprague-Dawley rats were randomly assigned to unstressed and stressed (chronic restraint stress) experimental groups. Afterward, animals were supplemented with n-3 PUFA (DHA and EPA mix) or vehicle. Dendritic morphology and synaptic transmission in the hippocampus were evaluated by Golgi stain and patch-clamp tools, respectively. The Morris water maze were used to analyze the effects of chronic stress on memory. ELISA and the plus-maze test were used to evaluate plasma corticosterone levels and anxiety as stress markers. Supplementation with n-3 improved dendritic architecture and restored the frequency of inhibitory postsynaptic currents of hippocampal pyramidal neurons of stressed rats. In addition, n-3 supplementation improved spatial memory and decreased corticosterone levels and anxiety of stressed rats. Our results demonstrate that n-3 supplementation had four beneficial effects on stressed rats: prevents dendritic atrophy in CA3, restores the GABA release probability in CA1, improves spatial memory, and a strong anti-stress property. We speculate

that ω-3 supplementation could be used in the treatment of stress-related psychiatric disorders such as depressive and anxiety disorders.

Disclosures: **A. Dagnino-Subiabre:** None. **M.A. Pérez:** None. **V. Peñaloza-Sancho:** None. **J. Ahumada:** None. **M. Fuenzalida:** None.

Poster

813. Circadian Entrainment and Phase Shift

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 813.01/X44

Topic: E.08. Biological Rhythms and Sleep

Title: The effects of wheel-running and monthly 6-hour advance on the progression of type-2 diabetes in C57Bl/6J and TallyHo/JngJ mice

Authors: *J. A. SEGGIO, J. A. HICKS, A. HATZIDIS, N. F. NASCIMENTO, K. N. CARLSON, N. L. ARRUDA, R. R. GELINEAU, I. K. MONTEIRO DE PINA, J. H. WEST; Biol. Sci., Bridgewater State Univ., Bridgewater, MA

Abstract: Type-2 Diabetes is the most common form of human diabetes, accounting for about 90% of cases and affecting about 23 million Americans. It is often accompanied by hyperglycemia and obesity. Diabetes has been linked to disruptions in the circadian rhythms of both the organism and specific organs as it can affect critical clock genes and can lead to an increased possibility of developing the disorder or exacerbating it. This study looked at the effects of voluntary exercise on parameters associated with diabetes and obesity, including blood glucose and insulin, in C57BL6/J (B6) and TallyHo/JngJ (TH) mice when experiencing an acute 6-hour advance shift. Two groups of each genotype of mice were kept in either a 12:12 LD cycle or a 6-hour advance simulated jet-lag; half of each strain received access to a running wheel while the other half were placed into a home cage, which can monitor locomotor activity without a wheel. 12-hour fasting glucose tolerance tests were conducted every four weeks starting at age-week eight until age-week 24. Additionally, insulin and lipid (i.e., cholesterols and triglycerides) levels were tested during the final shift. In LD conditions, early access to a running-wheel had no effect on the behavior or physiology of each mouse genotype; however, after prolonged exposure, TH mice exhibited reductions in blood lipids and insulin levels, and better glucose tolerance. Interestingly, TH mice undergoing the 6-hour advance, showed overall reduced insulin and blood lipid levels and lower glucose compared to TH mice in LD. Additionally, the running-wheel did not produce further improvements on insulin or glucose tolerance, as it did during LD. In addition, TH mice appeared to shift much more quickly to the new light phase compared to

B6. One possibility for the alteration in diabetic symptoms in TH mice is that the 6-hour shift leads to an alteration in the insulin secreting rhythm, which may promote circadian desynchrony between central and peripheral oscillators, when being subjected to jet-lag.

Disclosures: **J.A. Seggio:** None. **J.A. Hicks:** None. **A. Hatzidis:** None. **N.F. Nascimento:** None. **K.N. Carlson:** None. **N.L. Arruda:** None. **R.R. Gelineau:** None. **I.K. Monteiro De Pina:** None. **J.H. West:** None.

Poster

813. Circadian Entrainment and Phase Shift

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 813.02/X45

Topic: E.08. Biological Rhythms and Sleep

Support: DGAPA IN 200815

CONACyT 129-511

Title: Effects of obesity on the entrainment of circadian rhythms to light: The role of glutamatergic system

Authors: *V. P. CARMONA-ALCOCER[1,2], D. ALCANTARA-GONZALEZ[3], I. DELINT-RAMÍREZ[4], M. DÍAZ-MUÑOZ[2], C. MOLINA-AGUILAR[2], A. NIETO-POSADAS[3], B. ORDAZ[3], F. PEÑA-ORTEGA[3], H. VALENTE-GODINEZ[2];
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Abstract: Obesity is becoming an increasing problem in industrialized countries. Recent studies have linked obesity to changes in the circadian regulation. Circadian cycling disturbances such as reductions in nocturnal activity, an increase in the variability of the free-running period as well as alterations in photic resetting are associated with obesity. The aim of the present work was to elucidate whether obesity affects the glutamatergic system in the suprachiasmatic nucleus (SCN). We initially evaluated circadian locomotor activity and the phase response curve to light. Secondly, we measured expression levels of the glutamate receptor and neuronal activity. Male Wistar rats fed with regular diet and water (control) or sucrose 30% (obese model) for 7 months.

In our obese model, we found an increase in adipose tissue reflected in body mass gain, a wide range of metabolic disorders, such as hyperleptinaemia, and an increase in insulin levels. Moreover obese animals have a diminished response to light pulses at CT22. The loss of response to light pulses appears to indicate an alteration on the glutamatergic system or photo-induction of clock genes. Because an alteration in the glutamatergic systems impacts clock gene expression we next sought to investigate the first option. As a first approximation we quantified the levels of synaptic NMDA receptors (NR) on isolated synaptosomes of obese and control rats. Our results show a reduction in NR-2b expression after the light pulse in obese rats, which could explain the alteration in behavior. To our knowledge this is the first study to link metabolic disorders to alterations in glutamate receptors on the SCN.

Disclosures: V.P. Carmona-Alcocer: None. **D. Alcantara-Gonzalez:** None. **I. Delint-Ramírez:** None. **M. Díaz-Muñoz:** None. **C. Molina-Aguilar:** None. **A. Nieto-Posadas:** None. **B. Ordaz:** None. **F. Peña-Ortega:** None. **H. Valente-Godinez:** None.

Poster

813. Circadian Entrainment and Phase Shift

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Program#/Poster#: 813.03/X46

Topic: E.08. Biological Rhythms and Sleep

Support: a grant from the Knowledge Cluster Initiative from the Ministry of Education, Culture, Sports, Science, and Technology of Japan

Title: Effect of light therapy for type 2 diabetics with poorly controlled glycemia during the winter season

Authors: *H. HIRANO[1], H. NISHIKAWA[2], M. MATSUDA[2];
[1]Yamaguchi Univ. Org Univ. Edu, Yamaguchi, Japan; [2]Dept of Lab. Sciences, Grad. Sch. of Med., Yamaguchi Univ., Ube, Japan

Abstract: Background and aims: Light therapy (LT) has been used as a beneficial treatment for several diseases, including seasonal affective disorder (SAD) and circadian rhythm sleep disorders. SAD is a mood disorder characterized by recurring symptoms in autumn and winter with atypical features such as hypersomnia, increased appetite, and weight gain. Unless the amount of antihyperglycemic agent is increased, some diabetic patients experience great difficulty controlling their glycemia during days of short photoperiod. To evaluate the effects of LT on diabetes, a clinical investigation was conducted over six years. Materials and methods:

Three male subjects aged 45 to 58 and nine female subjects aged 59 to 78 were enrolled in this investigation. They had all been treated for type 2 diabetes for a period ranging 8 years to more than 40 years. LT was randomly started between November and January, and terminated in April or May. One subject received bright-light therapy (BLT). Another subject first received BLT, and then treatment was changed to dawn simulation (DS). The rest received DS. All subjects completed the Seasonal Pattern Assessment Questionnaire (SPAQ), and underwent a structured diagnostic interview for DSM-IV axis 1 disorders (SCID-1) at the beginning and end of LT, respectively. In addition to measurement of HbA1c every 4 weeks, they were asked about their satisfaction on the following quality of life (QOL)-related items: sleep, extreme cold, food restriction, mood, and activity. Results: Though no one had a history of psychiatric consultation or met diagnostic criteria for any type of mood disorders, results of SPAQ revealed that each of them showed seasonal variations in sleep length, social activity, mood, weight, appetite and energy level. Their Global Seasonality Score ranged from 2 to 15, and its mean and SEM were 7.08 ± 1.89. For eleven subjects, LT improved satisfaction with all types of QOL-related items. Furthermore, four subjects lost weight, and HbA1c values of seven subjects significantly decreased. Discussion & Conclusions: LT appears effective in improving both QOL and glycemic control of the patients. The precise mechanism causing the beneficial effects of LT for type 2 diabetics remains unexplained. Our current understanding is as follows: LT advances phase-delayed circadian rhythms of the enrolled subjects. LT-induced phase advance alters the functions of the autonomic nervous system towards a sympathetic predominance. Consequently, the basal metabolic rate of the diabetics is increased, resulting in an improvement of QOL, weight loss and decreases in HbA1c values. This is all likely to lead to increases in daily activity.

Disclosures: **H. Hirano:** None. **H. Nishikawa:** None. **M. Matsuda:** None.

Poster

813. Circadian Entrainment and Phase Shift

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 813.04/X47

Topic: E.08. Biological Rhythms and Sleep

Support: BBSRC

Title: Measuring the physiological cost of circadian desynchrony in mammals

Authors: A. C. WEST[1], *D. A. BECHTOLD[2];
[1]Fac. of Life Sci., The Univ. of Manchester, Manchester, United Kingdom; [2]Univ. Manchester, Manchester, United Kingdom

Abstract: Almost all organisms on the planet rely on intrinsic timekeeping mechanisms to anticipate fluctuations within the environment and adapt their physiology accordingly. Mammals are certainly no exception, and coordinated daily rhythms are evident in most aspects of our behaviour and physiology (e.g. from sleep/wake and feeding cycles to hormone rhythms and metabolism), all driven by a circadian clock network. The circadian clockwork is responsive to environmental signals (such as light/dark and food availability), which not only reinforces our synchronisation with the external environment, but also facilitates internal synchrony between brain and tissue clocks located across the body. Unfortunately, within our modern society the natural framework of perpetual and predictable environmental rhythmicity has been undermined. Indeed epidemiological evidence clearly associates shift-working patterns with cancer, immune dysfunction and numerous metabolic problems. The adaptive and fitness value of the circadian timing has been clearly demonstrated in lower organisms. However, the intrinsic value of the circadian system in mammals is less clear, and little is known of the underpinning biology that associates clock disruption with disease states. We therefore set out to define the impact of circadian misalignment in mice by imposing stable, but non-resonant (i.e. non-24hr) cycles of light and/or food. As expected, mice exhibited robust entrainment to environments that were within the limits of the circadian clock (e.g. 22.5hr to 27hr cycles). However, despite achieving stable entrainment, chronic exposure (>16 weeks) to non-resonant light/dark cycles resulted in widespread and tissue specific disruption of the molecular clockwork and downstream clock regulated transcriptional rhythms. Moreover, mice maintained in non-resonant light/dark cycles also exhibited a number of physiological consequences, including altered metabolic rate, reduced insulin sensitivity, and cardiac dysfunction. Together these studies highlight the profound impact of circadian misalignment on mammalian physiology, and provide mechanistic insight into the clock disruption-associated pathophysiology associated with circadian disruption in human populations (such as shift work and forced desynchrony).

Disclosures: **A.C. West:** None. **D.A. Bechtold:** None.

Poster

813. Circadian Entrainment and Phase Shift

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 813.05/X48

Topic: E.08. Biological Rhythms and Sleep

Support: NSF Grant IOS-11-18792

Title: Prenatal exposure to dim light at night impairs offspring delayed-type hypersensitivity reaction

Authors: *Y. M. CISSE, R. NELSON;
Neurosci., The Ohio State Univ. Wexner Med. Ctr., Columbus, OH

Abstract: Light is one of the most potent signals to the circadian system. Adoption of electrical lighting has occurred without consideration or understanding of the wide ranging physiological and psychological effects of light at night. Disruption of natural light/dark cycles by light at night (LAN) dampens endogenous biological rhythms to maintain optimal functioning of various organ systems and other bodily functions. The immune system, especially T cell proliferation and NK-cell activity, exhibits circadian rhythms in function. Dim LAN (dLAN) exposure impairs response to delayed type hypersensitivity (DTH), an antigen specific T-cell mediated immune response, in Siberian hamsters (*Phodopus sungorus*). Studies of the effects of LAN on immune function have thus far focused on adult immune function, but impaired maternal immune function has downstream effects on offspring immune phenotype. Thus, we hypothesized that parental exposure to dLAN impairs offspring immune function and decreases DTH responses in adult offspring. Adult (8 week) male and female Siberian hamsters were exposed to either dark or dimly lit nights (dLAN) for 9 weeks, at which point they were paired and mated in dark nights. Pairings resulted in four groups: Dark/Dark (M/F), Dark/Dim (M/F), Dim/Dark (M/F), and Dim/Dim (M/F). At 8 weeks of age, offspring underwent sensitization to 2-4-dinitro-1-fluorobenzene (DNFB) on the dorsum followed a week later by a secondary DNFB challenge on the pinna in order to assess DTH. Male offspring of mothers exposed to dLAN suppressed DTH mediated inflammation, suggesting impaired T cell function. Female offspring required both maternal and paternal exposure to dLAN to affect swelling 2 days after challenge. Decreased T-cell function in offspring that have only experienced dLAN in their germline suggests that seemingly innocuous, but pervasive, nighttime lighting may have long ranging effects on offspring fitness. Future studies will investigate circulating and splenic immune cell phenotype via flow cytometry.

Disclosures: **Y.M. Cisse:** None. **R. Nelson:** None.

Poster

813. Circadian Entrainment and Phase Shift

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 813.06/Y1

Topic: E.08. Biological Rhythms and Sleep

Support: UIUC Office of Undergraduate Research

Title: Impact of shift work on attention, female estrous cycling, and cholinergic signalling in a rat model

Authors: *M. B. LEVENTHAL, R. BALACHANDRAN, A. ROBERTSON, P. EUBIG, M. MAHONEY;
Univ. of Illinois Col. of Vet. Medic, Urbana, IL

Abstract: There has been a sharp rise in the number of shift workers- those who work outside of the normal "9 to 5" schedule. Because they work when they would normally be inactive, shift workers are faced with perturbed biological rhythms and increased risk for health conditions including cancer, diabetes, cardiovascular issues, obesity, and mood disorders. Furthermore, female shift workers face additional risks such as infertility and irregular reproductive cycles. There has been a strong focus on identifying how shift work affects physiological systems, however, relatively few studies have examined cognitive deficits caused by shift work and altered biological rhythms. Here we investigate how shift work-like schedules impact attention and whether there are sex differences in the response to shift work, attentional processes, and the interaction of these variables. We tested male and female Long Evans rats on a well-established behavioral measure of attention, the 5-choice serial reaction time task (5CSRTT). Animals were tested during their light phase (4 hours after lights-on) or during their dark phase (4 hours after lights-off) when they would be inactive or active, respectively. We analyzed daily wheel running activity patterns and female reproductive cycles. After test completion, brains were collected and stained for choline acetyltransferase (ChAT) in the nucleus basalis magnocellularis (nbm) and protein quantification of nicotinic acetylcholine receptors and ChAT in the medial prefrontal cortex (mPFC). These areas were selected because cholinergic projections from the nbm to the cortex have been shown to be important for 5CSRTT performance and involved in learning, memory, and arousal. Contrary to our hypothesis, animals that performed the 5CSRTT during the day, outside of their normal active phase made fewer incorrect responses, suggesting that they are more attentive. However, within day-tested animals, those that shifted to a diurnal activity pattern performed better than those that remained nocturnal. Furthermore, females tested during the day made fewer incorrect responses than male counterparts, indicating there is a sex difference in the impact of time of day on attention. Light-phase tested females had lengthened and irregular estrus cycles. The majority of experimental (9/12) and control animals (8/14) tested in the day became predominantly active during the light phase, demonstrating that 5CSRTT performance, as well as food cues alone, are capable of entraining activity. Finally, animals who were active during the light phase had increased numbers of ChAT-positive cells in the nbm compared to animals who were active during the dark phase.

Disclosures: **M.B. Leventhal:** None. **R. Balachandran:** None. **A. Robertson:** None. **P. Eubig:** None. **M. Mahoney:** None.

Poster

813. Circadian Entrainment and Phase Shift

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 813.07/Y2

Topic: E.08. Biological Rhythms and Sleep

Support: NSF IOS1354913

Title: Characterizing cerebellin-short, a novel circadian peptide, in the rat suprachiasmatic nucleus

Authors: *J. L. CHU[1], J. W. MITCHELL[1], M. U. GILLETTE[2];
[1]Cell. & Developmental Biol., [2]Neurosci. Program, Univ. Illinois Urbana-Champaign, Urbana, IL

Abstract: The suprachiasmatic nucleus (SCN), the central circadian clock in mammals, contains a number of peptides important for synchronizing the intrinsic rhythm and conveying it to other parts of the brain. Cerebellin-short (SGSAKVAFSAIRSTN) is a small peptide consisting of 15 amino acids identified in mass spectrometry proteomics to be secreted from the SCN in circadian fashion (Hatcher et al., PNAS, 2008). Cerebellin-short is the C-terminus histidine-truncated form of 16 amino acid full-length cerebellin, a peptide enriched in cerebellum (Slemmon et al., PNAS, 1984). The distribution and function of cerebellin-short in the SCN, however, are unknown. Here we show that Cbln1, the precursor for cerebellin, is expressed in the SCN with daily oscillations in mRNA and protein levels. Exogenous cerebellin-short applied at midday and early night phase advance the spontaneous firing rhythm of SCN neurons, suggesting that endogenous cerebellin-short contributes a circadian regulatory function. These findings present the possibility for the involvement of cerebellin-short in the intrinsic circadian timekeeping of SCN.

Disclosures: J.L. Chu: None. **J.W. Mitchell:** None. **M.U. Gillette:** None.

Poster

813. Circadian Entrainment and Phase Shift

Location: Hall A

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Program#/Poster#: 813.08/Y3

Topic: E.08. Biological Rhythms and Sleep

Support: Medical School Bridge Funding

Title: Intrinsically photosensitive retinal ganglion cells (ipRGCS) mediate light entrainment of peripheral clocks

Authors: *P. KOFUJI, N. PURRIER, S. MISHRA, W. C. ENGELAND;
Dept Neurosci, Univ. Minnesota, Minneapolis, MN

Abstract: The suprachiasmatic nucleus (SCN) in the hypothalamus houses the central circadian pacemaker and synchronizes autonomous circadian clocks in peripheral tissues to generate rhythms of metabolism and physiology. While the SCN biological clock follows an intrinsic period of ~24 hours, neurochemical signals from the retina provide photic information for the precise alignment of the SCN to environmental light-dark cycles. This photic information is conveyed by a subpopulation of retinal ganglion cells, intrinsically photosensitive retinal ganglion cells (ipRGCs), that express the photopigment melanopsin (Opn4) and therefore respond to light even in the absence of rod and cone photoreceptor input. It is still unclear whether ipRGCs are the sole pathway for photic entrainment of the peripheral clocks present in tissues throughout the body. In this study we have assessed the role of ipRGCs in synchronizing peripheral clocks to environmental light-dark cycles in mice. ipRGC neurotransmission was silenced by expression of tetanus toxin light chain fragment (TeNT) in melanopsin-expressing ganglion cells by crossing the $Opn4^{Cre/+}$ with $R26R^{TeNT/+}$ mouse line that has Cre recombinase-controlled expression of TeNT. As expected, non-image-forming visual behaviors such as the pupillary light reflex and photoentrainment of circadian locomotor activity were effectively abolished in $Opn4^{Cre/+}$, $R26R^{TeNT/+}$ mice; loss of photoentrainment resulted in "free-running" rhythms in locomotor activity. Moreover, light pulse-induced c-fos expression in the SCN was largely reduced in the mutant mice in comparison to littermate controls. The rhythmicity of peripheral clocks was monitored by intercrossing $Opn4^{Cre/+}$, $R26R^{TeNT/+}$ with $mPer2^{Luciferase}$ ($mPer2^{Luc}$) knockin mice. Both SCN and peripheral tissues from $Opn4^{Cre/+}$, $R26R^{TeNT/+}$, $Per2^{Luc/+}$mice showed robust and self-sustained circadian rhythms for several days in explant cultures; importantly, peak phase of PER2Luc rhythms was aligned with circadian locomotor activity, not environmental light-dark cycles. Likewise, using subcutaneous microdialysis probes to collect samples for corticosterone over several days, circadian glucocorticoid rhythms were observed to be “free running” in mutant mice. Overall these results indicate that ipRGCs are required for the synchronization of circadian clocks in peripheral tissues to environmental light-dark cycles.

Disclosures: **P. Kofuji:** None. **N. Purrier:** None. **S. Mishra:** None. **W.C. Engeland:** None.

Poster

813. Circadian Entrainment and Phase Shift

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Program#/Poster#: 813.09/Y4

Topic: E.08. Biological Rhythms and Sleep

Support: Wallin Discovery funds

NSF IOS1025199

NIH R01DK100653

Title: The adrenal clock acts as a buffer that prevents disruption of glucocorticoid rhythms by aberrant light exposure

Authors: *W. C. ENGELAND[1], S. MISHRA[1], P. KOFUJI[1], D. BREAULT[2];
[1]Neurosci, Univ. Minnesota, Minneapolis, MN; [2]Harvard Med. Sch., Boston, MA

Abstract: The circadian rhythm in adrenal glucocorticoid (GC) secretion provides the brain with a hormonal milieu that is critical for cognitive resiliency in the face of distress. The GC rhythm is entrained to light-dark (LD) cycles via a molecular clock in the suprachiasmatic nucleus (SCN) that is reset daily by photic signals and is maintained by an adrenal clock that is synchronized by SCN-dependent signals. Aberrant light exposure (e.g. light at night) observed during shift work or jet lag can disrupt the GC rhythm. To determine the requirement of the adrenal clock in stabilizing the circadian GC rhythm during exposure to an aberrant LD cycle, experiments were done using a novel adrenal clock KO mouse and microdialysis sampling to monitor corticosterone rhythmicity. We generated $AS^{Cre/+}$ :: $Bmal1^{fl/fl}$ :: $R26R^{mTom/mGFP/+}$ mice (adrenal clock KO) by intercrossing $AS^{Cre/+}$ mice (Cre recombinase inserted in the aldosterone synthase (AS) genetic locus) with the mT/mG Cre reporter and the floxed Bmal1 strains. In adult male and female wild-type (WT) mice, membrane bound green fluorescent protein (mGFP) expressed in adrenal cortex, but not medulla, was co-localized with nuclear BMAL1 labeling. In adult male and female KO mice, expression of mGFP was associated with loss of BMAL1 labeling. Mice implanted with subcutaneous microdialysis probes were sampled continuously at 30-60 min intervals for up to 3 days under both 12:12h (tau (T) 24) LD and 3.5:3.5h (T7) LD cycles, aberrant light exposure that produces a depressive-like phenotype in mice. Dialysate corticosterone was assayed by radioimmunoassay; rhythmicity was assessed using Pulsar analysis. Corticosterone rhythms remain entrained to a T24 LD cycle in WT and adrenal clock KO mice. Under a T7 LD cycle, a circadian rhythm in corticosterone persists in WT mice that is disrupted by intermittent corticosterone pulses. In contrast, circadian rhythms are abolished in adrenal clock KO mice under a T7 LD cycle due to corticosterone pulses that are magnified in

frequency and in amplitude. These data suggest that circadian GC rhythmicity under a T24 LD cycle is resistant to loss of the adrenal clock. In contrast, under a T7 LD cycle the adrenal clock is required to stabilize the circadian GC rhythm, buffering GC responses to aberrant light. Supported by Wallin Discovery funds, NSF IOS1025199 and NIH R01DK100653.

Disclosures: W.C. Engeland: None. **S. Mishra:** None. **P. Kofuji:** None. **D. Breault:** None.

Poster

813. Circadian Entrainment and Phase Shift

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 813.10/Y5

Topic: E.08. Biological Rhythms and Sleep

Support: PAPIIT, IN212715

Title: Ovariectomy shortens the period and increases photic phase shift of circadian locomotor activity rhythm in the mouse Neotomodon alstoni

Authors: C. R. JUÁREZ TAPIA, *M. MIRANDA-ANAYA, A. CARMONA-CASTRO, G. MARTÍNEZ-MORALES;
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Abstract: The Suprachiasmatic nucleus (SCN) is considered the master circadian pacemaker in mammals; it receives photic information mainly through the retino-hypothalamic tract and its effect on the oscillator depends on the phase of the cycle. A circadian oscillator exists in diverse tissues different than SCN, known as peripheral oscillators that are coordinated and feeds back to the SCN. The ovary is a peripheral oscillator in rodents and it produces hormones that influence the hypothalamus, including the regulation of the circadian rhythms. However, the mechanisms through which ovarian hormones impact such regulation have not been thoroughly studied. The effects of ovariectomy over circadian rhythms and its response to light seems to be different according to the species tested; in the present study we studied its effect on the circadian locomotor activity rhythm in the Mexican volcano mouse *Neotomodon alstoni.* Effects upon free running period, entrainment and photic phase shifting were tested. Adult females were used intact, sham surgery or ovariectomized. The circadian rhythm of locomotor activity was automatically registered in individual mice by means of infrared light beams and observed in constant darkness. Phase changes were induced by a 1 hour light (300 lx) pulse at Circadian Time (CT) 14 and CT22. The results show that ovariectomized females display shorter circadian period value and amplitude of the circadian rhythm of locomotor activity in free running than

sham or intact; circadian activity profile changes includes decreasing in amplitude and a biphasic pattern. The effect of a light pulse at CT14 shows greater phase shift delays in ovariectomized than the sham or intact but no differences were noted at CT22. The latter indicates that the ovaries, possibly through their hormones, influence period regulation and light sensitivity of the SCN in this species where estrogen profile along the estrous cycle is similar to traditional laboratory rodents.

Disclosures: C.R. Juárez Tapia: None. **M. Miranda-Anaya:** None. **A. Carmona-Castro:** None. **G. Martínez-Morales:** None.

Poster

813. Circadian Entrainment and Phase Shift

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Topic: E.08. Biological Rhythms and Sleep

Support: 2R25GM061151-13

Title: Simulating temperature cycles in the colony uncover chronotypes in honey bee foragers

Authors: *M. A. GIANNONI GUZMAN, J. ALEMAN-RIOS, T. GIRAY, J. L. AGOSTO-RIVERA;
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Abstract: Individual variation in diurnal preference in humans (chronotypes), have been correlated with differences in period length, circadian phase and other physiological measures. Furthermore, chronotypes have been associated with individual variation in different physiological and neurological processes as well as in the susceptibility to various diseases. We have previously shown large individual variation in the endogenous period length of honey bee foragers from the same colony. In this study we investigated the temporal pattern of light and temperature within honey bee colonies in the filed, simulated in the laboratory and determined its effectiveness as a as a potential Zeitgeber in the hive and whether individuals present differences in the circadian phase with respect to this time giver. To determine if temperature oscillates in a circadian manner within the colony, we placed data loggers throughout the colony to measure light and temperature. Our results show temperature oscillations that increase in amplitude as you move away from the core of the colony. To determine if these cycles are sufficient to entrain the circadian clock of honey bees, we simulated these cycles in our biological incubators in the laboratory. Our results show that these temperature cycles are indeed capable of entraining the

circadian clock. Surprisingly, we also found that there is individual variation in the circadian phase of individuals with respect to temperature and ranges from -6 hours to 2 hours, with more than 60% of the individuals having a phase between -2 and 0. Moreover, we found that advancing the temperature cycle by six hours, resulted in individual differences in the response to the environmental manipulation, such that some individuals adjusted to the new temperature regiment, while others didn't. Taken together our describe for the first time circadian chronotypes in honey bee foragers. In addition, we find that temperature is a potential Zeitgeber for honey bee foragers, but its relative contribution compared with light entrainment requires further examination. Studying the observed phase differences between the endogenous clock and temperature cycles could provide critical insight into how honey bee colonies manage and efficiently exploit resources available at specific times of the day.

Disclosures: M.A. Giannoni Guzman: None. **J. Aleman-Rios:** None. **T. Giray:** None. **J.L. Agosto-Rivera:** None.

Poster

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Support: NSF IOS-1021957

Title: Role of tissue-type plasminogen activator (tPA) in food anticipatory activity in mice fed one or two meals a day

Authors: *A. RASTOGI, E. M. MINTZ;
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Abstract: In rodents, the presence of food for only a few hours a day (one meal) results in the appearance of food anticipatory activity (FAA). They can also anticipate two meals per day, with FAA split between these meals. The underlying neural mechanism of FAA and its behavioral splitting in the case of two meals may differ from that of one meal, with the possible involvement of two different neuronal populations. To study this, two experiments were performed using memory deficient tissue-type plasminogen activator knock out (tPA-/-) male mice and wild type (tPA+/+, C57BL/6J) males. tPA-/- mice are severely deficient in long-term potentiation, long-term depression, and hippocampal-based learning and memory tasks. We have previously shown that these mice show increased FAA when presented a single period of food

availability per day. Mice were individually maintained in 12L:12D photoperiod with ad libitum food. After entraining to LD conditions, in the first experiment, mice (n=6) received either one meal of four hours at ZT6 (ZT0: lights onset) or continued in ad libitum, and perfused after 1 week at ZT5. In the second experiment, the LD cycle was changed to 18L:6D, and after two weeks in this condition, mice (n=12) received two meals (separating from 5 hours) of two hours each, at ZT5 and ZT12. After a week, mice were perfused (n=6 each time) either at ZT4 or at ZT11. Behavioral results suggest that with one meal mice lose 12-18% weight, although with two meals they lose 8-10% weight, which showed a better adaptation of mice with two meal timings. With one meal, FAA developed in all the mice with higher activity amplitude in tPA-/- than tPA+/+. Contrary to this, with two meals, tPA+/+ mice showed higher activity amplitude than tPA-/- with individual variations in FAA appearance between genotypes. With the 1st meal at ZT5, all mice developed FAA, though with the 2nd meal at ZT12, 58% tPA+/+ and 75% tPA-/- mice developed FAA. Our Fos-immunohistochemistry data suggests that in response to one meal, Fos expression in dorsomedial hypothalamus (DMH) and arcuate nucleus (ARC) increases several folds relative to ad libitum food condition. Contrary to this, under two meals, Fos expression dampens compared to one meal in DMH and ARC. Interestingly, Fos was equally expressed in DMH between genotypes, although in ARC expression was higher in tPA-/- than tPA+/+ between both meal timings. These data suggest that the mechanisms underlying FAA differ between the one and two-meal situations, and that the loss of tPA may limit adaptation to multiple periods of food availability per day.

Disclosures: **A. Rastogi:** None. **E.M. Mintz:** None.

Poster

813. Circadian Entrainment and Phase Shift

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Topic: E.08. Biological Rhythms and Sleep

Support: NSERC

Title: Investigating the role of ghrelin in food anticipatory activity of a scheduled treat

Authors: ***R. KHAZALL**, H. MACKAY, A. ABIZAID;
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Abstract: Food availability constitutes an environmental variable that can influence circadian rhythms. For instance, laboratory rodents exposed to restricted feeding schedules (i.e.schedules

where food is available only a few hours during the day) results in changes in locomotor activity that include an increase in locomotor activity in anticipation of the oncoming meal. Interestingly, these behaviours are not only expressed under negative energy balance. Exposure to palatable foods is also associated with increases in food anticipatory behavior in rats and mice. Ghrelin, a hormone associated with feeding and metabolism, has also been implicated in the expression of food anticipatory behavior in mice and rats, but it's not known if ghrelin is also associated with increased anticipatory behaviors to scheduled snacks. To determine if this is the case, we conducted experiments where male CD-1 mice were housed in locomotor activity boxes. After a 7 day baseline period of ad lib access to a standard laboratory chow, experimental mice were given daily 2hr access to commercial chocolate chip cookie dough in the middle of their light cycle (ZT6-ZT8) for 15 days. Results showed that experimental mice exhibited a significant increase in locomotor activity in anticipation of the cookie dough. This increase in anticipatory activity was maintained several days after access to the treat was terminated. The experimental mice also consumed more calories than controls, but did not gain more weight than controls, nor did they differ from the controls in plasma levels of glucose, corticosterone,or ghrelin. In a second experiment the experimental period was extended to 21 days and a 6 day re-exposure period was added, in which the animals were reintroduced to the cookie dough following the recovery period. As previously observed, mice that had limited access to cookie dough demonstrated a significant increase in anticipatory locomotor activity throughout the experimental period, which was maintained throughout recovery and was re-established during the re-exposure period. Body weight, food intake and plasma levels of ghrelin and glucose did not differ between the groups. These results suggest that CD-1 mice display robust locomotor activity in anticipation of a scheduled snack, and that behaviour continues for days following the last day of cookie dough exposure. The maintenance of treat anticipation after the cookie dough is no longer presented, however, is not associated with plasma ghrelin concentrations.

Disclosures: **R. Khazall:** None. **H. Mackay:** None. **A. Abizaid:** None.

Poster

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Topic: E.08. Biological Rhythms and Sleep

Support: CIHR MOP13625

Title: Circadian restricted feeding: effects of amphetamine sensitization and cross-sensitization

Authors: *H. N. OPIOL, S. RUTHERFORD, N. DE ZAVALIA, S. AMIR;
Psychology, Ctr. For Studies In Behavioral Neurobiology, Con, Montreal, QC, Canada

Abstract: Circadian restricted feeding (RF) is the application of daily timed feeding schedules that occur at the same time each day. RF shifts our internal 24h biological rhythms and behaviour. Dopamine is believed to be a key component in circadian RF. To test whether enhancing dopamine would also enhance behavioural properties of circadian feeding, rats underwent different amphetamine sensitization protocols and food anticipatory activity (FAA) was observed (between and within design). FAA is the behavioural hallmark of circadian RF that is defined as increased activity (e.g. running wheel) prior to feeding time once internal synchrony to feeding is achieved. Our study found no evidence for amphetamine sensitization on FAA. Further investigation suggested a ceiling effect between controls and amphetamine sensitized rats, such that RF itself could be causing behavioural sensitization. We hypothesized that behavioural sensitization was occurring during RF and perhaps continued after body weight had been restored. Studies by other labs have shown that caloric restriction results in dopamine-related enhancement, especially by increasing behavioural response to rewarding drugs. Though, these studies report the effects subside when free access to food and body weight are returned. Preliminary evidence from our lab indicated that cross-sensitization was present after body weight was restored. To test whether circadian RF could lead to cross-sensitization after body weight had been restored we placed rats on RF for 2 weeks then waited 10-14 days before giving an acute injection of amphetamine. Behaviour was measured using an open-field box. Results indicated that rats subjected to RF had a higher response to amphetamine than ad lib and saline controls. We then tested if behavioural cross-sensitization was specific to circadian RF or simply caloric restriction itself. Rats were divided into 2 groups: RF or variable RF that provided food at the same time or unpredictable time each day, respectively. Results indicated that cross-sensitization is not the result of caloric restriction itself; circadian scheduled feeding produced a significantly higher behavioural response than unpredictable RF, compared to controls. Finally, we tested whether daily scheduled access to a treat (no caloric restriction) would yield similar cross-sensitization to amphetamine, both under circadian and variable schedules- it did not. Our data indicate that circadian RF appears to be a unique feeding paradigm, requiring caloric restriction and the induction of circadian controlled oscillators that result in the maintenance of post-feeding behavioural cross-sensitization.

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Poster

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Title: GIRK channels mediate the nonphotic effects of exogenous melatonin

Authors: *L. M. HABLITZ[1], H. E. MOLZOF[2], K. L. GAMBLE[2];
[1]Univ. of Alabama At Birmingham, Birmingham, AL; [2]Psychiatry- Behavioral Neurobio., Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Melatonin supplementation has been used as a therapeutic agent for several diseases, yet little is known about the underlying molecular mechanisms by which melatonin acts within the brain to synchronize circadian rhythms. G protein signaling plays a large role in melatonin-induced phase shifts of locomotor behavior. Melatonin receptors have been shown to activate G protein-coupled inwardly-rectifying potassium (GIRK) channels in Xenopus oocytes. The present study tested the hypothesis that melatonin influences circadian phase and electrical activity within the clock center of the brain, the suprachiasmatic nucleus (SCN), through GIRK channel activation. The results showed that, unlike wild-type littermates, GIRK2 knockout mice failed to phase advance wheel-running behavior in response to 3-day subcutaneous injections of melatonin in the late day. Loose patch electrophysiological recordings of SCN neurons revealed a significant reduction in the average intrinsic action potential rate in response to melatonin. This effect was lost in the presence of a GIRK antagonist, tertiapin-q (TPQ), and in SCN neurons from GIRK2 knockout mice. The melatonin-induced suppression of firing rate corresponded with an increased inward current that was blocked by TPQ. Finally, application of ramelteon, a potent melatonin receptor agonist, also significantly decreased firing rate and increased inward current within SCN neurons in a GIRK-dependent manner. These results are the first to show that GIRK channels are necessary for the effects of melatonin and ramelteon within the SCN. This study suggests that GIRK channels may be an alternative therapeutic target for diseases with evidence of circadian disruption, including aberrant melatonin signaling.

Disclosures: L.M. Hablitz: None. **H.E. Molzof:** None. **K.L. Gamble:** None.

Poster

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Title: Using optogenetics to shift the circadian clock

Authors: *M. TACKENBERG[1], J. R. JONES[1], D. G. MCMAHON[2];
[1]Neurosci., [2]Biol. Sci., Vanderbilt Univ., Nashville, TN

Abstract: The mammalian biological clock, the suprachiasmatic nucleus (SCN), is composed of individual oscillators that maintain 24-hour rhythms in gene expression, firing rate, and peptide release. In the past, electrophysiological measurements and actigraphy, in combination with gene knockouts or modifications, have been used to determine the role of the each rhythmic "layer" of the SCN. These unidirectional techniques have given us a partial understanding of the interaction between gene, firing rate, and peptide release oscillations, but fall short of providing a complete picture of this system. To address this lack, we have developed an optogenetic system capable of initiating action potentials within the SCN with great temporal and spatial resolution, both *in vivo* and *in vitro*. By doing so in combination with real-time clock gene luminescence reporters *in vitro* and actigraphy *in vivo*, we have been able to measure the sufficiency of action potential generation throughout the SCN in shifting the circadian clock. We have found that, both *in vivo* and *in vitro*, action potential generation within the SCN is capable of producing circadian changes in locomotor behavior and gene expression, respectively. Interestingly, we have found that these changes are VIP-dependent and do not occur in the presence of TTX. Taken together, these results indicate that action potentials are both sufficient and necessary to produce phase shifts within the SCN. This information will provide us with a better approach for the future in determining the functional significance of SCN heterogeneity, that is, the differing role of action potentials within segregated populations of SCN neurons.

Disclosures: M. Tackenberg: None. **J.R. Jones:** None. **D.G. McMahon:** None.

Poster

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Support: NSF 1354913

Title: Redox state of the suprachiasmatic nucleus affects photic resetting in early night

Authors: ***M. YU**[1], Y. YU[2], J. W. MITCHELL[3], M. X. LU[4], M. U. GILLETTE[3];
[1]Mol. and Integrative Physiol., [2]Neurosci. Program, [3]Cell and Developmental Biol., Univ. of Illinois At Urbana Champaign, Urbana, IL; [4]Univ. of Illinois Lab. High Sch., Urbana, IL

Abstract: The main driver of circadian behavior is a transcriptional-translational feedback loop of core circadian genes. Emerging evidence suggests that metabolic oscillators also play a crucial role in circadian rhythm generation. The discovery of a near-24h oscillation of redox state in the suprachiasmatic nucleus (SCN) has put metabolism in the center of circadian biology (Wang et al. Science 2012), yet little is known about what drives the redox rhythm or the extent of its influence in the SCN. The mammalian circadian clock is especially sensitive to photic signals and can adjust its phasing in response to retinal light exposure during the night. This response to light is biphasic: exposure to light during the early night results in a phase delay in behavioral rhythms, whereas exposure to light during the late night results in a phase advance in the rhythms. In this study, we examined the relative redox states of the rat SCN in early and late night by western blot analysis for glutathiolation and found a more oxidized state in early night and a more reduced state in late night. Using single-unit recording techniques to assess phasing of the neuronal activity rhythm in SCN brain slices, we found that changing the redox environment in early night altered the directionality of phase shifting in response to glutamate, the messenger of the light signal from the retina to the SCN. To determine the effect of redox state on photic resetting in early night in intact animals, we performed intra-SCN cannulation surgery on male C57Bl/6 mice and injected glutathione (GSH), a natural reducing agent, directly into the SCN at circadian time (CT) 14 followed immediately by a light pulse. The onset of wheel running activity in constant dark conditions was used to evaluate effects on phasing of behavioral rhythms. We found that GSH blocked the usual light-induced phase delay in the early night, while the vehicle had no effect. These results suggest that flipping the SCN redox state from oxidized to reduced can block the photic resetting response in early night, providing further evidence that the redox rhythm may play a regulatory role in circadian physiology.

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Poster

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NIH F31NS086282

Title: Glycogen synthase kinase 3 (GSK3) regulates light signaling in the suprachiasmatic nucleus

Authors: *J. R. PAUL, S. K. TOTSCH, R. M. COWELL, K. L. GAMBLE;
Dept. of Psychiatry and Behavioral Neurobio., Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: Glycogen synthase kinase 3 (GSK3) regulates light signaling in the suprachiasmatic nucleus Paul, J.R., Totsch, S.K., Cowell, R.M., and Gamble, K.L. Glycogen synthase kinase 3 (GSK3) is a serine-threonine kinase that is an emerging regulator of mammalian circadian rhythms at the behavioral, molecular and neurophysiological levels. In the central circadian pacemaker, the suprachiasmatic nucleus (SCN), GSK3 exhibits a rhythm in inhibitory phosphorylation across the 24h day. We have recently shown that GSK3 is capable of influencing both the molecular clock and SCN neuronal activity rhythms. However, whether GSK3 regulates the response to environmental cues such as light is not yet known. The goal of this project was to test the hypothesis that GSK3 activation mediates light-induced SCN excitability and photic entrainment. Immunofluorescence staining in the SCN showed that late-night light exposure significantly increased GSK3 activity (i.e., decreased p-GSK3β levels) 30-60 minutes after the light-pulse. Additionally, pharmacological inhibition of GSK3 blocked the typical light-induced excitability in *Per1*::GFP expressing SCN neurons; however, this effect was not associated with changes in resting membrane potential or input resistance. Behaviorally, mice with constitutively active GSK3 (GSK3-KI) re-entrained significantly more rapidly to a 6-hour phase-advance than WT control animals. Furthermore, GSK3-KI mice had a significantly advanced phase-angle of entrainment when released into constant darkness, which mimicked the effect of a 1-hour light pulse in WT mice. Finally, GSK3-KI mice exhibited normal negative-masking behavior, suggesting that the enhanced photic entrainment is not due to an overall increased sensitivity to light in these animals. Taken together, these results provide strong evidence that GSK3 activation contributes to light-induced phase-resetting at both the neurophysiological and behavioral levels. Given that GSK3 dysregulation has been implicated in multiple disorders that have also been associated with chronic light at night, such as depression,

obesity, and cancer, a better understanding the effects of light on GSK3, and its role in regulating SCN neurophysiology could provide new treatment strategies for these disorders in the future. This work was supported by NIH 1R01NS082413 to KLG and F31NS086282 to JRP.

Disclosures: J.R. Paul: None. **S.K. Totsch:** None. **R.M. Cowell:** None. **K.L. Gamble:** None.

Poster

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Topic: E.08. Biological Rhythms and Sleep

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Title: Activation of the stress axis is associated with novel wheel-induced blockade of the luteinizing hormone (LH) surge in Syrian hamsters

Authors: *S. J. LEGAN[1], X. PENG[2], M. J. DUNCAN[3];
[1]Dept Physiol, [2]Dept Physiol., [3]Dept Anat. and Neurobio., Univ. of Kentucky, Lexington, KY

Abstract: Circadian rhythm desynchrony, which is common in shift workers, is associated with decreased fertility in women. In proestrous hamsters, arousal induced by a novel wheel (NW) and transfer to constant darkness (DD) in the mid-day usually blocks the preovulatory LH surge that day and phase-advances its occurrence the next day (Legan et al., 2010). A locked NW also blocks the LH surge, suggesting that intense running is not required for this phenomenon. Exposure to a NW (either locked or freely turning) also activates orexin neurons, and antagonism of orexin receptors prevents NW blockade of the LH surge (Duncan et al., 2014). These results suggest that arousal/wakefulness plays a major role in the mechanism whereby non-photic stimuli suppress LH surges. This is supported by the finding that exposing estradiol benzoate (EB)-treated ovariectomized (ovx) hamsters to arousal using toys also suppresses and delays LH surges, similar to the effect of a NW (Legan et al., 2015). Therefore we tested the hypotheses that: (1) presenting a NW in the middle of the day transiently activates the stress axis, and (2) that blockade of the LH surge is associated with the magnitude of the resultant increase in corticosterone (CORT) levels. Diestrous hamsters and ovx hamsters treated s.c. with EB were surgically fitted with jugular cannulae. The next day at zeitgeber time (ZT) 5 (ZT 12=lights off), after obtaining a baseline blood sample, each hamster was exposed to DD and either returned to her home cage (HC) or transferred to a new cage with a NW. Serial blood samples were taken hourly until ZT 11 in red light. Activity was monitored in DD for 1-2 weeks. Plasma LH and

CORT concentrations were assessed by RIA. Phase advances in the activity rhythm did not differ among the groups (HC, 4.5 ± 0.4 h; NW proestrous, 3.3 ± 0.3 h; NW ovx+EB, 3.1 ± 0. 6 h; P=0.06). LH surges were blocked in 6 of 12 HC hamsters. In contrast, a NW blocked the LH surge in 10 of 12 proestrous hamsters and greatly attenuated it in all 7 ovx+EB hamsters. In HC hamsters, plasma CORT concentrations remained low regardless of whether an LH surge occurred. In contrast, CORT levels rose about 2-fold above baseline for ~2 h only in the 10 NW-exposed hamsters in which the LH surge was blocked, and remained unchanged in the 2 hamsters whose LH surge was not blocked. Interestingly, the suppression of the LH surge in the ovx+EB hamsters was associated with a 1-h elevation in plasma CORT. Thus the effectiveness of the NW in blocking or suppressing the LH surge is associated with the duration of its stimulation of plasma CORT levels. These results suggest that activation of the stress axis is part of the mechanism by which acute arousal blocks the LH surge.

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Poster

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Topic: E.08. Biological Rhythms and Sleep

Title: Role of the CREB-CRE signalling pathway on the crayfish Procambarus clarkii's locomotor activity rhythm entrainment

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Abstract: Recent findings in vertebrates show that an increase in the intracellular cAMP may play a role in the light entrainment pathway in the suprachiasmatic nucleus of the rat brain. The cAMP activation of the CREB-CRE signalling pathway, promotes changes in the clock genes per1 and tim expression that ultimately produces a phase shift of the locomotor activity rhythm in the animal. Little is known about the signal transduction pathways in entrainment by light of the circadian system of invertebrates like the crayfish Procambarus clarkii. To address this question, we recorded the crayfish locomotor activity rhythm before and after the stimulation by light (300 lx) or the injection of a cAMP analog (db-cAMP) or a PKA antagonist (H89) at 3 different circadian times (CT13, CT10 and CT23). Results show that the light stimulus (control) induces phase delays of about 4 h at CT13 and phase advances of 4 h at CT23 and no significant changes at CT10. The db-cAMP injections induces similar changes as the light pulses. The

protocol for the PKA inhibitor, includes the injection of H89 1 h before the light pulse for each of the CT explored. In this way, PKA was inhibited before the light activated the cAMP signalling pathway. The results showed that the locomotor rhythm is disrupted by the H89 but in some cases there was phase shifts with magnitude and direction different of those produced by light and the cAMP analog. We conclude that the light may be signalling the molecular clock of the crayfish by activating the cAMP pathway and probably inducing changes in per and tim clock genes that control the period and phase of the clock in the animal's brain.

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Poster

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College of Charleston, Office of Undergraduate Research and Creative Activities

Title: Biological rhythms in an invertebrate model marine organism, the Starlet Sea Anemone

Authors: *E. L. MEYER-BERNSTEIN[1,2], W. D. HENDRICKS[2], C. C. JAMES[2], E. E. MCPHERSON[2,1], M. R. JAMES[2,1];
[1]Honors Col., [2]Biol., Col. of Charleston, Charleston, SC

Abstract: Animals display rhythms in physiology and behavior that are governed by a self-sustaining biological clock. Environmental stimuli serve to synchronize an animal’s clock at the molecular level, which leads to correlated changes in behavior. Rhythmic behavior is primarily driven by daily photic signals in most organisms, but can also be influenced by other non-photic environmental stimuli such as temperature and food availability. A concerted effort has led to significant progress in elucidating biological clocks at the behavioral, cellular and molecular level in terrestrial organisms. However, marine organisms, particularly invertebrates, are not well-studied and, consequently, our understanding of the rhythms in such species is comparatively underdeveloped. Considerable attention has also been placed on understanding the molecular clockwork underlying circadian rhythmicity; However, the regulation of non-circadian rhythms (i.e. tidal, lunar) remains unclear. Moreover, signals that drive these rhythms and their integration with the circadian clock have not been thoroughly investigated. Intertidal organisms

may provide a means to develop our understanding of biological rhythms in marine organisms as well as an opportunity to advance our knowledge of rhythms with a diversity of frequencies. Intertidal organisms are particularly interesting as their behavior can be synchronized to a variety of stimuli (light, temperature, hydrostatic pressure, salinity, etc), some of which cycle with periods other than 24 hours. Our laboratory is developing the starlet sea anemone, Nematostella vectensis, as a model organism for the study of biological rhythms. We previously established a circadian rhythm in body column elongation in this species. We have continued our efforts on the localization of circadian gene expression and cellular identification as well as the behavioral and molecular synchronization by photic, temperature and tidal stimuli. Our anatomical data indicate a localization of canonical circadian gene expression in the oral disk and tentacles that is closely associated with GABAergic cells. Behavioral synchronization to non-photic stimuli was observed with accompanying changes in critical molecular components. Outcomes of these experiments will allow us to better understand the potential interactions between multiple sensory stimuli that impact rhythmic behavior and the underlying molecular components in this evolutionarily informative species.

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Brain Kore 21 Plus

Title: Advanced circadian phase in manic episode was returned to normal after treatment in bipolar disorder

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Abstract: ***Objective:*** Bipolar disorder (BD) is a common mental disorder that causes pathological shifts in mood, activity, and energy levels. We observed behavioral and molecular circadian rhythms in severe manic states and in recovery states in hospitalized patients with BD, and compared them with those of healthy participants. ***Methods:*** Included in the study were 24 manic episodes of 21 type I BD patients (12 male and 9 female) who were hospitalized in from May 2012 to June 2014, and 18 healthy subjects (11 male and 7 female). The age of the subjects [mean ± SEM] was 30.0 ± 2.3 years for patients in mania, 23.0 ± 0.8 years for the control group. To assess the circadian rhythms of activity, actigraphy data were obtained by actiwatch from all participants. From healthy participants, sample collections of salivary and buccal epithelial cells were performed at 8:00, 11:00, 15:00, 19:00, and 23:00 for two consecutive days. From BP patients, sample collections were performed in the same schedule with healthy participants and repeated with 2 weeks intervals during hospitalization and right before discharge. Collected salivary samples were used for cortisol assay and each participant's cortisol circadian rhythm were determined. mRNA was isolated from collected buccal epithelial cells, and the rhythms of circadian genes were determined as a ratio of *Per1*/*Bmal1* expression. Paired t-test were used as appropriate to assess the significance of differences between groups. ***Results:*** Mean treatment duration of the BP patients was 24.6 ± 2.6 (SEM) days. For cortisol circadian rhythms, the average acrophase of each BD patients in the severe manic states were significantly advanced compared to the healthy controls (p = 5.43E-07) by the amount of 8h 40m. In contrast, the acrophases in recovered euthymic states were not significantly different from those of healthy controls (P>0.05). For the ratio of *Per1*/*Bmal1* circadian rhythm, the average acrophase of each BD patients in the severe manic states was significantly advanced compared to the healthy controls (p = 1.35E-08) by the amount of 11h 13m. Whereas, the acrophases in recovered euthymic states were not significantly different from those of healthy controls (P>0.05). Actigraphy data indicated no significant difference in circadian rhythm of activity between manic and euthymic states. ***Conclusions:*** Molecular circadian rhythm in severe manic episodes of BD patients was significantly advanced compared to healthy controls. After the treatment, the advanced rhythm was changed to normal. This finding provides a means for our understanding of the mechanisms of the circadian rhythm of the BD.

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Poster

813. Circadian Entrainment and Phase Shift

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 813.23/Y18

Topic: E.08. Biological Rhythms and Sleep

Support: NSERC

Title: Assessment of molecules involved in circadian rhythms and memory in the hippocampi of circadian rhythm disrupted rats

Authors: *S. H. DEIBEL[1], D. KOCHAN[2], J. Q. LEE[1], R. J. KEELEY[1], K. M. NIEDERMEIER[1], I. BARKLEY[1], N. S. HONG[1], O. KOVALCHUK[2], R. J. MCDONALD[1]; [1]Canadian Ctr. for Behavioural Neuroscience, Neurosci., [2]Dept. of Biol. Sci., Univ. of Lethbridge, Lethbridge, AB, Canada

Abstract: There is a large body of evidence in rodents suggesting that circadian rhythm dysfunction (disruption) impairs memory. In rats, we have demonstrated that circadian rhythm disruption induced by acute or chronic photoperiod shifting elicits memory impairments in hippocampal-dependent memory tasks. It appears that these impairments are due to disrupted memory consolidation, however, the mechanisms mediating this effect are largely unknown. Clock genes, and molecules involved in synaptic plasticity and epigenetics oscillate in the hippocampus. While unknown, it is likely that the oscillations of these molecules are disrupted in the hippocampi of circadian rhythm-disrupted animals. The present study assessed clock gene expression, clock protein expression, and sirtuin1 - a histone deacteylase enzyme involved in circadian rhythms and memory - in the hippocampi of photoperiod shifted rats. We anticipate that the phase of the oscillations of these rhythmically expressed molecules will be shifted in the circadian rhythm-disrupted animals, but it is possible that this effect will be dependent on the length of the photoperiod shifting paradigm. Preliminary data suggests that the phase of CLOCK protein expression in the hippocampus is unaffected by a brief amount of photoperiod shifting. These data will contribute to the elucidation of the mechanisms underlying the memory impairment induced by circadian rhythm disruption.

Disclosures: **S.H. Deibel:** None. **D. Kochan:** None. **J.Q. Lee:** None. **R.J. Keeley:** None. **K.M. Niedermeier:** None. **I. Barkley:** None. **N.S. Hong:** None. **O. Kovalchuk:** None. **R.J. McDonald:** None.

Poster

814. Sleep: Regulators

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Topic: E.08. Biological Rhythms and Sleep

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Title: Time-dependent changes of deta power across NREM sleep episodes in mice

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Abstract: Sleep is homeostatically regulated. Delta power increases and promotes the drive to sleep after sleep debt, and decreases following sleep duration. Generally, delta power is averaged over a NREM sleep episode and indicates the need for sleep. In this study, we investigated details of the time-dependent changes of delta power across NREM sleep episodes after sleep deprivation. C57/bl6 mice were implanted with EEG/EMG electrodes, allowed to recover for 10 days, habituated to the recording environment for 21 days, and then used for sleep experiments. All sleep deprivation was employed from ZT0-6. Each of the sleep deprivation experiments was separated by at least 21 days. Baseline EEG/EMG activities were monitored on the day before each sleep deprivation experiment. Sleep state were scored in 10-second epochs. For all conditions, delta power in NREM sleep episodes between 0-12 min in ZT6-8 were collected for each mouse and averaged in 10-second bins. These data were then averaged across mice. In the baseline condition, delta power was constant between 0-10 min in an average NREM sleep episode. Furthermore, this constant delta power was observed in any average NREM sleep episode during light or dark phases, or 24-h durations in the baseline condition. After 6-h acute sleep deprivation using a treadmill, significant increase of delta power was observed mainly in the onset of an average NREM sleep episode (< 4 min). This delta power elevation in an average NREM sleep episode was similarly observed in mice following 6-h spontaneous wakefulness induced by approaching novel objects. Consecutive 5-day chronic sleep restriction (sleep deprivation during ZT0-6 using a treadmill) evoked a greater delta power increase in an average NREM sleep episode (< 8 min) compared with the baseline condition. These observations suggest that (1) the delta power level in a NREM sleep episode is constant in normal sleep conditions, and (2) sleep pressure accumulation prolongs delta power elevation within a NREM sleep episode.

Disclosures: A. Suzuki: None. **R.W. Greene:** None.

Poster

814. Sleep: Regulators

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Topic: E.08. Biological Rhythms and Sleep

Support: CONACYT-128392 (LBP) SUBVENCION

CONACYT-153627 (CMV) SUBVENCION

Title: Effect of selective Rapid Eye Movement (REM) sleep deprivation on c-Fos immunoreactivity in the ventral respiratory column in rat

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Abstract: In mammals, breathing and sleep are vital behaviors necessary for survival. Breathing is a continuous process to maintaining gas homeostasis whereas sleep is necessary to restore the homeostasis of the central nervous system. These behaviors are controlled by neurons in specific areas of the brainstem. Here, by using c-Fos immunoreactivity as a marker of neuronal activity, we examined the effect of selective REM sleep deprivation on activity of neurons from brainstem areas related to breathing such as the ventral respiratory column (VRC) and the parafacial respiratory group (pFRG/RTN). Male Wistar rats were divided in two groups: control (n=6) and selectively-deprived of REM sleep using the flowerpot technique (n=11). Respiratory rate, heart rate, temperature and oxygen saturation (SpO2) were measured before and during deprivation. No differences were found in the number of c-Fos positive neurons in the VRC and pFRG/RTN in the selectively REM sleep deprived group compared to control. In conclusion we suggest that activity of VRC and pFRG/RTN neurons is highly regulated during sleep to ensuring a stable breathing rate and gas homeostasis.

Disclosures: E. Muñoz Ortiz: None. **R. Diaz-Escarcega:** None. **C.A. Perez-Estudillo:** None. **F. Garcia-Garcia:** None. **L. Beltran-Parrazal:** None. **C. Morgado-Valle:** None.

Poster

814. Sleep: Regulators

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Topic: E.08. Biological Rhythms and Sleep

Support: JSPS KAKENHI Grant-in-Aid for JSPS Fellows: Grant Number 15J00393

JSPS KAKENHI Grant-in-Aid for Young Scientists (B): Grant Number 15K18966

Title: Identification of a single nucleotide substitution specific to the Dreamless mutant mouse pedigree by linkage analysis and whole exome sequencing, and its genetic verification by CRISPR

Authors: ***T. FUJIYAMA**[1], C. MIYOSHI[1], M. SATO[2], T. KANDA[1], S. MIZUNO[2], S. TAKAHASHI[2], H. MURAMOTO[1], K. IWASAKI[1], F. ASANO[1], T. HONDA[1], A. IKKYU[1], M. KAKIZAKI[1], N. HOTTA[1], S. KANNO[1], Y. ISHIKAWA[1], I. MIURA[3], T. SUZUKI[3], S. WAKANA[3], K. VIVEK[4], J. S. TAKAHASHI[4], H. FUNATO[1], M. YANAGISAWA[1];
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Abstract: Although sleep is a ubiquitous animal behavior, the molecular mechanism of sleep homeostasis remains unknown. We performed high-throughput screening of ENU-mutagenized mice in order to identify genes regulating sleep/wake behavior. We have so far analyzed EEG/EMG data of more than 7,000 mutagenized male mice. We established several pedigrees showing heritable sleep/wakefulness abnormalities. Among them, the Dreamless mutant pedigree shows about 50% reduction in 24-h REM sleep time. To map a chromosomal region responsible for the sleep phenotype of Dreamless mutant mice, we performed a linkage analysis in N2 mice, obtained by backcrossing the mutagenized founder C57BL/6J male to C57BL/6N female mice for two generations. The analysis revealed a single peak with a LOD score of more than 11. Whole exome sequencing of mutants and wild-type littermates from the Dreamless pedigree identified a nucleotide change specific to Dreamless mutant mice within the mapped chromosomal region. The single nucleotide substitution leads a single amino acid substitution of the gene product that we termed Dreamless. We adopted CRISPR/Cas system for reproduction of Dreamless phenotype and confirmed that the one base substitution was responsible for REM sleep abnormality. Functional analyses of the Dreamless gene are now underway.

Table 1. Sleep/wakefulness parameters of CRISPR-*Dreamless* mice (at 2~3 months age)

	Wakefulness			NREM sleep			REM sleep		
Period	*Dreamless* $^{+/+}$	*Dreamless* $^{m/+}$	*P*	*Dreamless* $^{+/+}$	*Dreamless* $^{m/+}$	*P*	*Dreamless* $^{+/+}$	*Dreamless* $^{m/+}$	*P*
24 h									
Time (min)	787.5 ± 15.4	762.9 ± 27.5	0.406	581.7 ± 15.0	633.8 ± 27.1	0.083	70.4 ± 3.4	43.3 ± 3.0	2.9E-05
Duration (s)	1003 ± 91.6	693.5 ± 42.6	0.013	400.7 ± 24.8	326.7 ± 30.9	0.079	84.0 ± 1.6	48.5 ± 6.8	9.9E-04
Frequency (episode/h)	2.15 ± 0.19	2.82 ± 0.19	0.033	3.81 ± 0.28	5.07 ± 0.37	0.013	2.10 ± 0.11	2.40 ± 0.21	0.194
REM sleep latency (min)							7.81 ± 0.47	6.52 ± 0.81	0.157
12-h light period									
Time (min)	228.0 ± 7.4	229.2 ± 12.7	0.933	434.3 ± 7.5	455.1 ± 12.9	0.150	57.7 ± 2.9	35.7 ± 2.0	2.7E-05
Duration (s)	428.5 ± 33.2	351.5 ± 48.8	0.192	396.9 ± 23.6	327.9 ± 33.4	0.099	84.5 ± 1.9	49.4 ± 6.9	1.2E-03
Frequency (episode/h)	2.81 ± 0.20	3.65 ± 0.46	0.126	5.69 ± 0.33	7.49 ± 0.80	0.066	3.43 ± 0.18	3.98 ± 0.43	0.256
REM sleep latency (min)							7.54 ± 0.44	6.34 ± 0.83	0.175
12-h dark period									
Time (min)	559.5 ± 9.9	533.7 ± 23.3	0.334	147.4 ± 9.3	178.7 ± 22.4	0.228	12.7 ± 1.1	7.6 ± 1.5	0.0114
Duration (s)	2433 ± 355.3	1492 ± 193.9	0.032	420.7 ± 37.2	339.0 ± 26.1	0.132	82.1 ± 3.0	46.0 ± 6.6	1.9E-05
Frequency (episode/h)	1.49 ± 0.23	1.95 ± 0.19	0.180	1.98 ± 0.28	2.59 ± 0.22	0.139	0.78 ± 0.07	0.80 ± 0.09	0.865
REM sleep latency (min)							8.92 ± 0.73	7.90 ± 0.82	0.380

Data are expressed as mean ± SEM for *Dreamless* $^{+/+}$ mice (n = 13, males) and *Dreamless* $^{m/+}$ mice (n = 8, males). All parameters were derived from EEG/EMG recordings for two consecutive 24-h periods. Statistical comparisons are by Student's t test. Significant changes ($P < 0.05$) are shown in colored.

* $P < 0.05$
** $P < 0.01$
*** $P < 0.001$

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Poster

814. Sleep: Regulators

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 814.04/Y22

Topic: E.08. Biological Rhythms and Sleep

Support: CIHR MOP-136969

CIHR MOP-136967

NSERC 298475

Title: Thalamic modulation of the cortical slow oscillation

Authors: *A. OZUR, S. CHAUVETTE, I. TIMOFEEV;
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Abstract: Despite recent progress, the role and mechanisms of sleep and the origin of the synchronous sleep slow oscillation remain a controversial topic. The slow/delta power is one of the main quantifiable parameters characterizing the quality of sleep. The thalamus is involved in slow-wave activity. However, the role played by the various thalamic nuclei in the generation of the slow oscillation and its synchronization is not known. We hypothesized that the first-order (specific) thalamic nuclei provide a control of slow waves in primary cortical areas, while high-order (non-specific) thalamic nuclei may synchronize the slow-wave activities across wide cortical regions. We analyzed local field potentials (LFP) and spiking activities from different cortical and thalamic areas of anesthetized mice while a thalamic nucleus was inactivated by either the sodium channel blocker QX-314 or the GABA-agonist muscimol. Extracellular multiunit recordings in specific (VPM, VL) and non-specific (PO, CL) thalamic nuclei show a dramatically decreased overall spiking activity and a strongly reduced burst firing after muscimol or QX-314 inactivation. We conclude that the injection of muscimol strongly reduced the spiking activity and does not potentiate the generation of low-threshold spike mediated bursts. Inactivation of specific thalamic nuclei (VL, VPM) with muscimol decreased the power of the slow/delta band in the corresponding primary cortical area while the injection of QX-314 reduced the slow/delta power in larger territories. The inactivation of a non-specific nucleus (CL/CM) with muscimol significantly reduced the delta power in all investigated cortical areas

and the effect was even stronger after the injection of QX-314. Our experiments demonstrate that the thalamus is required for the fine tuning of the cortical slow oscillation. Generally, the use of QX-314 affected larger cortical territories as compared to muscimol, likely because it affected not only local neurons but also passing fibers. We conclude that the non-specific thalamic nuclei play a major role in the regulation of the global cortical slow-wave activity.

Disclosures: **A. Ozur:** None. **S. Chauvette:** None. **I. Timofeev:** None.

Poster

814. Sleep: Regulators

Location: Hall A

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Topic: E.08. Biological Rhythms and Sleep

Support: European Union (FP7 SWITCHBOX Project)

Title: Programming of sleep disturbances by peripubertal diet-induced obesity - Implication of altered serotonergic actions in the brain

Authors: M. GAZEA, A. V. PATCHEV, E. ANDERZHANOVA, E. LEIDMAA, A. PISSIOTI, C. FLACHSKAMM, O. F. X. ALMEIDA, *M. KIMURA;
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Abstract: Overconsumption of palatable foods is the main driver of obesity, a condition affecting a large number of adolescents. Recent work shows that early-life obesity may amplify health risks in later life. Obesity and sleep disorders often accompany each other in a variety of medical conditions. While the causal link between obesity and sleep disturbances is unknown, it plausibly involves altered setpoints in the hedonic mechanism regulating eating behavior and the homoeostatic control in both feeding and sleep-wake behaviors. This hypothesis was here examined in the context of obesity during peripubertal development. Our mouse model of peripubertal diet-induced obesity (ppDIO) was generated by feeding male C57BL/6N mice a high-fat diet (HFD) between postnatal weeks 4 and 10. Cessation of HFD was followed by a standard diet (SD). EEG/EMG recordings were performed at different ages (10, 12, 24 and 52 weeks). In addition, neurotransmitter and neuropeptide levels in areas related to reward, feeding and sleep-wake regulation were evaluated. Mice that were maintained on SD served as controls. Chronic HFD exposure led to a hypo-dopaminergic and hypo-serotonergic state in ppDIO mice as compared to controls. These changes were accompanied by sleep fragmentation during the resting phase and increased sleep time during the active period. Cessation of HFD and re-

exposure to SD resulted in bodyweight loss and a dramatic reduction in sleep time during the active phase below those observed in control mice. Concomitant with HFD withdrawal, dopamine levels in reward-related areas were reduced, while serotonin levels in the lateral hypothalamus were increased; the latter area is an important integrator of sleep-wake and feeding behaviors. Interestingly, aged ppDIO mice (52 weeks) showed increased nocturnal sleep time in parallel with a hypo-serotonergic tone in the lateral hypothalamus. Sleep disturbances observed in both young and aged mice were rescued by i.p. injection of PYY3-36, a peripheral satiety hormone. In conclusion, ppDIO has marked effects on the long-term regulation of sleep-wake behaviors. Our results suggest that reduced serotonergic tone underlies sleep disturbances associated with obesity. During weight loss following HFD withdrawal, serotonergic tone increases, which may produce increased vigilance. Lastly, PYY3-36 has the potential to ameliorate sleep disturbances triggered by ppDIO.

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Poster

814. Sleep: Regulators

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Topic: E.08. Biological Rhythms and Sleep

Support: Medical Research Council, UK

BBSRC

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Title: Wakefulness is governed by GABA and histamine co-transmission

Authors: *X. YU[1], Z. YE[1], C. M. HOUSTON[1], A. Y. ZECHARIA[1], Y. MA[1], Z. ZHANG[1], D. S. UYGUN[1], S. PARKER[1], A. L. VYSSOTSKI[2], R. YUSTOS[1], N. P. FRANKS[1], S. G. BRICKLEY[1], W. WISDEN[1];
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Abstract: Histaminergic neurons in the tuberomammilary nucleus (TMN) of the hypothalamus form a widely projecting, wake-active network that sustains arousal. Yet most histaminergic neurons contain GABA. Selective siRNA knockdown of the vesicular GABA transporter (vgat, SLC32A1) in histaminergic neurons produced hyperactive mice with an exceptional amount of sustained wakefulness. Ablation of the vgat gene throughout the TMN further sharpened this phenotype. Optogenetic stimulation in the caudate-putamen and neocortex of "histaminergic" axonal projections from the TMN evoked tonic (extrasynaptic) GABAA receptor Cl- currents onto medium spiny neurons and pyramidal neurons. These currents were abolished following vgat gene removal from the TMN area. Thus wake-active histaminergic neurons generate a paracrine GABAergic signal that serves to provide a brake on over-activation from histamine, but could also increase the precision of neocortical processing. The long-range of histamine-GABA axonal projections suggests that extrasynaptic inhibition will be coordinated over large neocortical and striatal areas.

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Poster

814. Sleep: Regulators

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Topic: E.08. Biological Rhythms and Sleep

Support: Human Frontiers Science Program (RGP0004/2013)

Title: Ontogeny of activation in sleep and waking regulatory systems in the chick

Authors: ***M. POMPEIANO**[1], A. CHAN[1], S. LI[1], N. RATTENBORG[2], E. BALABAN[1], D. MARTINEZ-GONZALEZ[2];
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Abstract: In adult rodents, wakefulness is sustained by activity in an interconnected set of neuronal populations (the "arousal systems"), which includes hypocretin/orexin (H/O), noradrenergic Locus Coeruleus (NA-LC), serotonergic Dorsal Raphe (5HT-DR) and pontine cholinergic (Ch-P) neurons. Sleep is supported by activity in various GABAergic neuronal populations, and a lack of activity in the arousal systems. Rapid eye movement (REM) sleep is

supported by activation of Ch-P and melanin-concentrating hormone (MCH) neurons. Birds and mammals show similar sleep and waking states (Lesku and Rattenborg 2014). Chickens are precocial; they develop sleep-like electroencephalographic (EEG) patterns before hatching, and a stable waking state within a few hours after hatching (Mellor and Diesch 2007; Martinez-Gonzalez et al 2012). In order to understand when activity in neuronal populations that regulate sleep and waking becomes coordinated and able to support stable states, we investigated activity in the H/O, NA/LC, 5HT/DR, Ch-P and MCH systems of undisturbed chick embryos, and in neonatal (P1) chicks that were spontaneously sleeping or kept awake by gentle handling. cFos was used as a marker of neuronal activation. Fertilized eggs were incubated at 37.5° C, 55-60% relative humidity. Embryos (in ovo) and hatchlings were anesthetized (isoflurane) and intracardially perfused with fixative. Cryostat-cut sections were processed using standard fluorescent double labelling techniques. Stereological techniques were used to calculate the percentage of cFos-expressing cells in the 5 groups of neuronal populations. In general, activation of the arousal systems was low at embryonic day (E) 12, slowly increased at E16 and E20 and reached its highest values in the awake P1 chicks. Very low values were seen in sleeping P1 chicks. Activation of MCH neurons also progressively increased in embryos, reached its highest values at E20, but was low in both awake and sleeping P1 chicks. Among neuronal populations, significantly correlated activity was seen only between NA-LC and 5HT-DR cFos expression in embryos, and among most arousal systems at P1. We conclude that the arousal systems become progressively recruited in embryos and become coordinated only after hatching. MCH neurons may be involved in the emergence of REM sleep-like in chick embryos. Absence of activation of the Ch-P and MCH systems in the sleeping postnatal chicks may be due to the relatively short duration of the sleep episodes studied here.

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Poster

814. Sleep: Regulators

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Support: CIHR Grant MOP-93673

NSERC Grant 217301-2009

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Title: Sleep history modulates excitatory transmission to orexin and melanin concentrating hormone neurons via glial glutamate transporter 1

Authors: *C. L. BRIGGS[1,2], K. SEMBA[1], M. HIRASAWA[2];
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Abstract: Orexin (ORX) and melanin concentrating hormone (MCH) neurons of the lateral hypothalamus play important roles in sleep/wake behaviour. These neurons have opposite activity patterns, where ORX neurons are wake-active and MCH neurons sleep-active, suggesting that their regulatory mechanisms are also reciprocally active. We previously determined that the amount of astrocytic glutamate transporter 1 (GLT1) surrounding these neurons is altered by prior sleep history; acute 6h sleep deprivation (SD) decreased GLT1 surrounding ORX neurons and increased it surrounding MCH neurons. Glutamatergic transmission is shaped by glutamate transporters. We therefore asked whether sleep history affects GLT1 modulation of excitatory transmission to these neurons, using whole-cell recording in acute brain slices obtained from 6h SD or time-matched rested rats. In the rested condition, the GLT1 inhibitor DHK significantly reduced the amplitude of evoked excitatory postsynaptic currents (eEPSCs) in ORX neurons while increasing paired-pulse ratio (PPR), suggesting presynaptic inhibition. These effects were blocked by the group III metabotropic glutamate receptor (mGluR) antagonist CPPG while mimicked by the agonist L-AP4. CPPG alone did not alter eEPSC amplitude or PPR, indicating no tonic presynaptic inhibition. Following SD, the effects of DHK on eEPSC amplitude and PPR were largely eliminated. This appears to be an occlusion by endogenous glutamate tonically activating group III mGluRs, since application of CPPG alone decreased PPR. These results indicate that GLT1 facilitates excitatory transmission to ORX neurons specifically in rested conditions by preventing activation of presynaptic mGluRs. In contrast, we found no effect of DHK on eEPSC amplitude or PPR in MCH neurons from rested rats. However, following SD, DHK significantly reduced eEPSC amplitude (mechanism under investigation). These results indicate that GLT1 has no role in modulating fast excitatory transmission to MCH neurons in rested conditions, but facilitates excitatory transmission specifically in SD conditions. In conclusion, within a single hypothalamic area, astrocytes can differentially modulate two neuronal populations through GLT1. This regulation is opposite for ORX and MCH neurons in accordance with their roles in sleep/wake behaviour, dependent on sleep history, and in line with our anatomical results. GLT1 facilitates excitatory transmission specifically when GLT1 coverage is high, by limiting glutamate spillover and presynaptic activation of inhibitory autoreceptors. This may be a novel homeostatic mechanism for the control of sleep/wake behaviour.

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Poster

814. Sleep: Regulators

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Title: Conditional knockdown of tyrosine hydroxylase in LC neurons increases REM sleep by withdrawal of inhibition from PPT neurons and prevents REM sleep-loss associated expression in rats

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Abstract: Sleep, an instinct behavior, has been divided into rapid eye movement sleep (REMS) and non-REMS. The REMS has been preserved through evolution and species; however, its detailed mechanism of regulation and function(s) are yet unknown. Notwithstanding, it is known that there are REM-ON neurons (active during REMS) in pedunculopontine tegmental (PPT) and REM-OFF neurons (cease firing during REMS) in the locus coeruleus (LC); cessation of the REM-OFF neurons is a necessity for REMS generation. The noradrenalin (NA)-ergic REM-OFF neurons in the LC inhibit the PPT REM-ON neurons and prevent appearance of REMS. It has been reported that the REM-OFF neurons continue activity during REMS deprivation (REMSD) and if those neurons are kept active, REMS does not appear. Further, continuous activity of REM-OFF neurons would elevate NA level in the brain. Although isolated independent studies showed that elevated NA indeed reduced REMS and induced many of the REMSD associated symptoms, the detailed mechanism and direct evidence thereof were lacking. Therefore, in this study, NA synthesis was inhibited by conditionally down regulating tyrosine hydroxylase (TH) gene expression in the NA-ergic LC neurons using TH-siRNA/TH-shRNA and the effects on REMS and REMSD associated expressions were evaluated. Materials and Methods: Male Wistar rats (250-350g) were surgically prepared for chronic electrophysiological sleep-waking recording with simultaneous bilateral microinjection into either or both, LC and PPT. TH was knocked down in the LC neurons to reduce NA synthesis and REMS was estimated with or without infusion of NA bilaterally into the PPT. In other groups TH knock down rats were REMS deprived for 4 days. TH knock down in LC neurons was confirmed by counting TH immunostained neurons, quantitative PCR and Western blotting of LC. Results: Microinjection of TH-shRNA into LC significantly decreased TH-mRNA and TH protein in LC. TH-shRNA/TH-siRNA microinjection into LC significantly increased the total time spent in REMS

and the effect was prevented if NA was simultaneously injected into the PPT. Further, if such conditional NA-depleted rats were REMS deprived, Na-K ATPase activity was not increased, which was increased in otherwise REMSD rat brain. Conclusion: The results provide direct evidence that NA from LC neurons inhibits the REM-ON neurons and prevents REMS. Further, the NA released from the LC neurons is responsible for inducing REMSD associated expression. These findings confirm our hypothesis and are proof of principle for ameliorating REMS loss associated symptoms.

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Poster

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Title: Cortical nNOS/NK1 neurons are regulated by adenosinergic tone

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Abstract: Cortical neuronal nitric oxide synthase (nNOS) neurons that express the neurokinin-1 (NK1) receptor may play a role in sleep homeostasis (Kilduff et al. 2011 *TiNS*; Morairty et al 2013; *PNAS*). As nNOS/NK1 neurons appear to sense sleep need (Dittrich et al 2015; *Neuropsychopharmacol*) and as adenosine (ADO) is an indicator for sleep pressure, we investigated whether ADO affects nNOS/NK1 cells *in vitro* and examined the role for ADO receptors on recovery from sleep deprivation (SD). We prepared mouse brain slices (250μm) for whole-cell patch clamp recording and identified cortical nNOS/NK1 cells with substance P-tetramethylrhodamine (SP-TMR), a fluorescent agonist for NK1 receptors. Bath applied ADO (50μM) evoked either an outward (n=5) or inward current (n=8) in most cells. Both responses were retained in the presence of TTX (n=13 and n=14, respectively), indicating direct postsynaptic action. Changes in the resting membrane potential (RMP) of nNOS/NK1 cells induced by ADO were inhibitory (n=12) or excitatory (n=20); some neurons (n=8) lacked a response to ADO. The A1R antagonist DPCPX (3μM) blocked the inhibitory effects on RMP (n=5) and outward current (n=4). However, application of the A2R antagonist DMPX (10μM)

only blocked excitatory responses on RMP (n= 4 of 7) or current (n=2 of 5) in some cells. The $A2_AR$ agonist CGS21680 (30nm) evoked RMP depolarization (n=6) and inward current (n=6). ADO also affected both sEPSCs (n=10) and mEPSCs (n=14) onto nNOS/NK1 neurons, indicating presynaptic A1 and A2 receptors. When ADO was applied in the presence of the adenosine deaminase inhibitor EHNA, RMP inhibition (n=5) and excitation (n=2) occurred with concomitant outward or inward currents. The response to ADO receptor blockade changed if mice were given 4h SD prior to sacrifice. The magnitude of response to A1R blockade with DPCPX resulted in an inward current (n=5) and increased RMP (n=3) which were >100% greater than in mice without prior SD; responses to A2R blockade with DMPX was largely unchanged. These observations suggest that different subsets of nNOS/NK1 cells may be preferentially controlled by ADO. We tested the *in vivo* response of $A2_AR$ KO mice to 4h SD followed by a 4h recovery sleep (RS) "opportunity" on EEG parameters. The A1R antagonist CPT (9mg/kg, ip) administered before SD did not affect the percent of, or latency to, NREM sleep during RS in WT or $A2_AR$ KO mice (n=3). In contrast, the selective $A2_BR$ antagonist MRS1754 (0.5mg/kg) increased NREM latency during RS in $A2_AR$ KOs compared to WTs but increased % NREM during RS in WTs. These data support a role for A2Rs in sleep control and suggest ADO may act to fine-tune cortical activation and slow wave activity via nNOS/NK1 cells.

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Poster

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Topic: E.08. Biological Rhythms and Sleep

Title: Identification of discrete, intermingled hypocretin neuronal populations

Authors: M. IYER, *M. CARTER;
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Abstract: Neurons in the lateral hypothalamus that express hypocretin (Hcrt) neuropeptides are known to play roles in wakefulness and reward-seeking behaviors. To address these two potentially dichotomous functions, it has been proposed that Hcrt neurons can be functionally subdivided into at least two populations: one population forms a “medial group,” which regulates wakefulness by projecting to wake-promoting populations such as the noradrenergic locus

coeruleus (LC) and histaminergic tuberomammilary nucleus (TMN); the other population forms a "lateral group," which regulates reward-seeking by projecting to the dopaminergic ventral tegmental area (VTA) or nucleus accumbens (NAc). This hypothesis was initially supported by the finding that hypocretin neurons can be functionally subdivided into at least two populations based on their electrophysiological properties. However, retrograde tracers injected into either the LC or VTA do not seem to preferentially label either electrically active subclass of Hcrt neurons, nor do they preferentially label a medial or lateral population. To resolve whether Hcrt neurons can be anatomically subdivided into medial and lateral subpopulations, we injected fluorescent retrograde tracers into two downstream populations of Hcrt neurons in the same animal. A red tracer was injected into either the LC or TMN while a green tracer was injected into either the VTA or NAc. We found that red retrograde signal in Hcrt neurons from the LC or TMN rarely overlapped with green retrograde signal from the VTA or NAc, indicating that Hcrt neurons that project to wake-promoting or reward-promoting areas are anatomically distinct. Interestingly, we found no side preference for Hcrt neurons based on their downstream targets. These results suggest there are intermingled populations of Hcrt neurons that can be anatomically subdivided based on their downstream projections.

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Poster

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Title: Instantaneous and persistent arousal induced by bilateral optogenetic and pharmacogenetic excitation of HCRT neurons

Authors: *J. E. HEISS[1,2], T. S. KILDUFF[1], A. YAMANAKA[2];
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Abstract: HCRT (Orexin) neurons located in the lateral hypothalamus are a key regulator of arousal; loss of this neuronal group leads to the sleep disorder narcolepsy. HCRT cells provide

excitatory input to noradrenergic, histaminergic and serotonergic neurons, thereby regulating their activity and influencing the global state of the brain. In addition to the Hcrt1 and Hcrt2 peptides, HCRT neurons can release glutamate and dynorphin and perhaps other unknown neurotransmitters. *In vitro* studies have shown that HCRT neurons can induce brief glutamate-mediated excitation and persistent HCRT-mediated depolarization of histaminergic neurons. *In vivo* optogenetic studies have shown that unilateral stimulation of HCRT neurons during REM and NREM sleep induces an increase in the probability of awakening that is mediated by HCRT peptide release. To test whether brief stimulation of a larger population of HCRT neurons has a more robust effect on arousal than previously reported, we performed single pulse, bilateral optogenetic excitation of HCRT neurons in Orexin/tTA;TetO Chr2 (C128S) mice which constitutively express a "step function" opsin in HCRT neurons that is activated by a single pulse of blue light (475 nm) and inactivated by yellow light (575 nm). All manipulations described below were performed in the middle of the day (around ZT 6). In a pilot study (N=4 mice), a single 50 ms pulse of blue light flanked by a 200 ms yellow light pulse 50 ms before and 30 s later was delivered 1 mm above both HCRT fields. Blue light flanked by yellow pulses was alternated with yellow light flanked by yellow pulses (control) every 2 min for 30 min. Blue light stimulation induced awakening within 4 s after stimulation in over 75% of the trials. In contrast, the probability of a NREM-Wake transition was 20% for control trials. To determine whether prolonged stimulation of larger populations of HCRT neurons affects arousal, we injected Orexin/tTA mice with AAV-TetO-hM3Dq-mCherry bilaterally. Persistent pharmacogenetic stimulation of HCRT neurons by CNO injection (0.5-3 mg/Kg, IP) induced prolonged wakefulness that lasted 2-4 h (N=4). In the presence of the dual orexin receptor antagonist almorexant (200 mg/Kg, IP), preliminary data shows that the effect of optogenetic excitation of HCRT cells was unaffected (N=3) whereas the effects of persistent excitation mediated by hM3Dq DREADD was attenuated (N=3). Our results suggest that direct excitation of large populations of HCRT neurons is sufficient to induce wakefulness with a very short latency and that persistent, but not brief, arousal is mediated at least partially by HCRT peptides.

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Poster

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Topic: E.08. Biological Rhythms and Sleep

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Title: Orexin neurons suppress narcolepsy via 2 distinct efferent pathways

Authors: *E. HASEGAWA[1], M. YANAGISAWA[2], T. SAKURAI[1], M. MIEDA[1];
[1]Kanazawa Univ., Ishikawa, Japan; [2]IIIS, Tukuba Univ., Ibaraki, Japan

Abstract: The loss of orexin neurons in humans is associated with the sleep disorder narcolepsy, which is characterized by excessive daytime sleepiness and cataplexy. Mice lacking orexin peptides, orexin neurons, or orexin receptors recapitulate human narcolepsy phenotypes, further highlighting a critical role for orexin signaling in the maintenance of wakefulness. Despite the known role of orexin neurons in narcolepsy, the precise neural mechanisms downstream of these neurons remain unknown. We found that targeted restoration of orexin receptor expression in the dorsal raphe (DR) and in the locus coeruleus (LC) of mice lacking orexin receptors inhibited cataplexy-like episodes and pathological fragmentation of wakefulness (i.e., sleepiness), respectively. The suppression of cataplexy-like episodes correlated with the number of serotonergic neurons restored with orexin receptor expression in the DR, while the consolidation of fragmented wakefulness correlated with the number of noradrenergic neurons restored in the LC. Furthermore, pharmacogenetic activation of these neurons using designer receptor exclusively activated by designer drug (DREADD) technology ameliorated narcolepsy in mice lacking orexin neurons (orexin/ataxin-3 mice). These results suggest that DR serotonergic and LC noradrenergic neurons play differential roles in orexin neuron-dependent regulation of sleep/wakefulness. As a next step, we are aiming to identify the target area that mediates anti-cataplectic effects of activating DR serotonergic neurons. For this purpose, channelrhodopsin 2 was expressed specifically in DR serotonergic neurons by focal injection of a Cre-dependent AAV expression vector in the DR of SERT-Cre;orexin/ataxin-3 mice. Acute optogenetic activation of DR serotonergic neurons suppressed cataplexy-like episodes. Currently, we are searching serotonergic terminals that suppress cataplexy-like episodes upon their optogenetic activation.

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Poster

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Topic: E.08. Biological Rhythms and Sleep

Support: CIHR

NIH

Title: Role of cholinergic and GABAergic pontomesencephalic neurons in theta generation studied by optogenetic manipulation in naturally waking/sleeping head-fixed mice

Authors: Y. CISSÉ[1], H. TOOSSI[1], M. ISHIBASHI[2], L. MAINVILLE[1], A. ADAMANTIDIS[3], C. LEONARD[2], *B. E. JONES[1];
[1]Neurol. & Neurosurg., McGill Univ., Montreal, QC, Canada; [2]Physiol., New York Med. Col., Valhalla, NY; [3]Neurol., Univ. of Bern, Bern, Switzerland

Abstract: Cholinergic neurons in the pontomesencephalic tegmentum are thought to play an important role in modulating cortical activity across the sleep-waking cycle. Distributed in the laterodorsal and sublaterodorsal tegmental nuclei (LDT and SubLDT), cholinergic neurons lie intermingled with GABAergic neurons which could also modulate cortical activity. Through application of optogenetics, we sought to determine if tonic or phasic excitation of these cholinergic or GABAergic neurons could elicit theta activity in limbic cortex. Using ChAT-ChR-EYFP or VGAT-ChR-EYFP expressing transgenic mice, we confirmed in brain slices by whole-cell recordings that light pulses evoked photocurrents sufficient to drive repetitive firing selectively in cholinergic and GABAergic neurons respectively. In urethane-anesthetized transgenic mice, photostimulation allowed the *in vivo* identification of cholinergic or GABAergic neurons by short latency spike elicitation and thereby recording along with excitation of these specific cells in association with EEG activity. As previously reported (Cisse et al., SfN, 2013), light-evoked firing by the cholinergic neurons and also GABAergic neurons was associated with a shift from irregular slow to rhythmic slow (theta-like) activity under urethane. Here, using the same optogenetic approach, we sought to record from and modulate identified cholinergic and GABAergic LDT/SubLDT neurons in naturally waking/sleeping, head-fixed transgenic mice. Photo-identified during recording, neurons were also labeled with Neurobiotin using the juxtacellular technique and their location and identity confirmed using immunofluorescent staining for ChAT or GABA. Identified cholinergic neurons discharged spontaneously in a slow tonic manner in association with cortical activation and when photo-excited from relative silence during EEG slow wave activity and sleep to their maximal rate, elicited cortical activation characterized by theta activity along with increased gamma activity. GABAergic neurons discharged spontaneously in a fast phasic manner in association with cortical activation and when photo-excited from minimal discharge during slow wave sleep with phasic theta pulsed stimulation, elicited theta activity with increased gamma. Our findings suggest that cholinergic and GABAergic LDT/SubLDT neurons can serve collectively to promote theta activity along with increased gamma and transition from slow wave sleep to wakefulness or paradoxical sleep (PS or REM sleep).

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Poster

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Topic: E.08. Biological Rhythms and Sleep

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Title: Chronic inflammation of the preoptic-hypothalamic sleep-regulatory systems induces aging-like changes in sleep-wake organization in young rats

Authors: A. KOSTIN[1], M. ALAM[1], R. SZYMUSIAK[1,2], D. MCGINTY[1,3], *N. ALAM[1,2]; [1]Res. Service (151A3), VAGLAHS, Sepulveda, CA; [2]Dept. of Med., University of California, Los Angeles, CA; [3]Dept. of Psychology, University of California, Los Angeles, CA

Abstract: INTRODUCTION: Sleep disturbance is a significant problem of advancing age and includes more frequent awakenings, decreases in nonREM and REM sleep amounts and nonREM slow wave activity and increases in daytime sleepiness. Both animal and human studies indicate that the brains in older subjects are in a native heightened inflammatory state, even in the absence of overt disease. Evidence also suggests that chronic inflammatory processes play a role in cellular aging including neuronal aging. We examined effects of chronic inflammation of sleep-regulatory preoptic-hypothalamic median preoptic nucleus (MnPN) and ventrolateral preoptic area (VLPO) on sleep-wake organization in young rats. METHOD: Three months old Fisher 344 male rats were implanted with EEG and EMG electrodes for chronic recording of sleep-wake states and with a guide cannula targeting at MnPN or VLPO for the delivery of artificial cerebrospinal fluid (aCSF) or lipopolysaccharides (LPS) using an alzet mini-osmotic pump. The sleep-wake profiles of rats were recorded during baseline (without any treatment) and during chronic infusion of aCSF (n=1, MnPN) or LPS (0.11µg/h) for 2 weeks into the MnPN (n=2) or VLPO (n=2). At the end, the sites of drug delivery were histologically confirmed. RESULTS: The data analyzed after 4 days of treatment shows that during the lights-on phase (inactive period), as compared to the baseline/aCSF control, chronic LPS infusion into the MnPN of young rats decreased both nonREM (54 ± 3% vs. 40 ± 4%) and REM sleep (11 ± 2% vs. 5 ± 1%) and increased sleep fragmentation as marked by increases in number of sleep episodes (28 ± 2 vs. 34 ± 6) and frequent awakenings (11 ± 2 vs. 16 ± 6). On the other hand, during the dark-phase (active period) waking was decreased (77 ± 1% vs. 62 ± 8%) and marked by increased sleep intrusions (15 ± 2 vs. 22 ± 1). An initial review of the sleep-wake records indicates that these effects persisted during the last days of treatment. Chronic LPS infusion into the VLPO produced similar changes in sleep-wake organization. CONCLUSION: LPS-induced chronic

inflammation of the MnPN and VLPO in young rats produces sleep-wake features that are similar to those observed in aging. Although the underlying mechanisms remain unknown, these preliminary findings suggest that chronic inflammation of sleep-regulatory MnPN and VLPO may play a role in sleep disturbance that accompany aging.

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Poster

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Title: Shared striatal subnetworks relevant for stress, sleep, and Huntington's disease implicate TGFβ-FOXO3 signaling

Authors: *J. R. SCARPA[1], P. JIANG[2], K. FITZPATRICK[2], B. LOSIC[1], V. D. GAO[2], K. HAO[1], K. C. SUMMA[2], B. ZHANG[1], R. ALLADA[2], M. H. VITATERNA[2], F. W. TUREK[2], A. KASARSKIS[1];
[1]Genomics, Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Northwestern Univ., Evanston, IL

Abstract: Recent systems-based analyses have demonstrated that sleep and stress traits emerge from shared genetic and transcriptional networks(Jiang et al., 2015), and clinical and experimental work have elucidated the emergence of sleep dysfunction and stress susceptibility in neurodegenerative disease. In the present work, we specifically examine the relationship between these psychiatric traits and Huntington's disease (HD) by identifying striatal transcriptional networks shared by HD, stress, and sleep phenotypes. Using a public microarray dataset (GSE3790), we identified a caudate network that is differentially connected in HD

compared to controls and is enriched for previously identified sets of differentially expressed HD genes (Durrenberger et al., 2014; Hodges et al., 2006). Further analysis revealed that this HD-relevant network is enriched specifically for astrocyte gene signatures (Cahoy et al., 2008; Lein et al., 2007). We used multiple public experimental datasets (GSE60137, GSE13347, GSE18326) to demonstrate that this astrocyte HD network is downstream of a signaling pathway important in adult neurogenesis (TGFβ-FOXO3). We then mapped this HD-relevant caudate subnetwork to striatal transcriptional networks in a large (n=100) chronically stressed (B6xA/J)F2 mouse population that has been extensively phenotyped (328 stress- and sleep-related measurements). We identified the causal regulators of this mouse subnetwork through Bayesian network analysis, and we verified their relevance to HD, sleep, and stress through multiple in silico approaches, including an examination of their protein interaction network. Lastly, we suggest that these causal regulators may be therapeutically viable for HD because their downstream network is partially modulated by deep brain stimulation, a medical intervention thought to confer some therapeutic benefit to HD patients(Gruber et al., 2014; Zielonka et al., 2014). By analyzing and integrating multiple independent datasets, we identify a point of molecular convergence between sleep, stress, and HD that reflects their phenotypic comorbidity and supports a fundamental mechanism of neuropathogenesis.

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Poster

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Title: Gene networks in mouse striatum reveal links between sleep, stress, neuropsychiatric disorders and neurodegeneration

Authors: ***P. JIANG**[1], J. R. SCARPA[2], K. FITZPATRICK[1], B. LOSIC[2], V. D. GAO[1], K. HAO[2], K. C. SUMMA[1], B. ZHANG[2], R. ALLADA[1], M. H. VITATERNA[1], A. KASARSKIS[2], F. W. TUREK[1];
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Abstract: An accumulating body of literature has documented comorbidities of sleep dysfunction, stress susceptibility and a range of neuropsychiatric and neurodegenerative disorders. However, molecular pathways and networks underlying such connections remain largely unknown. Our previous work screened a large number of complex phenotypes (N = 328) relevant for sleep and stress in a large population of chronically stressed (C57BL/6J x A/J) F2 mice. We utilized multi-scale approaches integrating phenotypic, genotypic and gene expression data in the striatum, and identified gene regulatory networks underlying sleep, stress and their interactions. This provides a rich resource for further exploration of the links between sleep, stress, health and disease. Here, by integrating genetic and gene expression signatures of neuropsychiatric and neurodegeneration disorders, we show that a number of striatal networks associated with multiple sleep and stress phenotypes are also enriched with or even causally driven by genes important for neuropsychiatric and neurodegenerative disorders. For example, we show that a cellular stress response network associated with sleep after acute restraint stress is driven by a GWAS candidate gene for attention-deficit/hyperactivity disorder. Similar overlapping between causal regulators of sleep/stress networks and GWAS candidate genes for neuropsychiatric disorders is prevalent, and thus it may suggest a common feature for gene networks underlying sleep and stress. We also show that a microglia/immune network enriched with GWAS and gene expression signatures of Parkinson's disease is strongly associated with EEG activities during sleep, highlighting the links between inflammatory signaling, sleep and neurodegeneration. In summary, our findings recapitulated phenotypic comorbidities between stress, sleep and central nervous system disorders, and suggest the interplay between sleep, stress, and neuropathology emerge from genetic influences on gene expression and their collective organization through complex molecular networks.

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Poster

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Title: Optogenetic regulation of parvalbumin (PV) GABAergic neurons in thalamic reticular nucleus (TRN) in control of cortical spindle generation and its implications in schizophrenia

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Abstract: Sleep spindles (8-15Hz) are waxing and waning EEG patterns observed during light non-REM sleep. Recent studies in schizophrenia (Sz) patients have provided consistent evidence for abnormalities in the number and intrinsic frequency of sleep spindles, together with associated cognitive problems. Sleep spindles originate in the thalamic reticular nucleus (TRN) that contains GABAergic neurons, most of which are parvalbumin (PV) positive. A plausible but untested hypothesis is that sleep spindle abnormalities are due to down regulation of the activity of TRN PV neurons, either due to intrinsic deficits or due to changes in afferent inputs. One major, likely inhibitory, input comes from wake-promoting basal forebrain (BF) PV neurons. Thus, here we test the effect on spindles by optogenetic manipulation of both TRN PV neurons and afferent inputs from BF PV neurons. Experiments were performed in mice that express Cre recombinase in PV neurons (PV-Cre). The selective activation or inhibition of TRN PV neurons was performed using channelrhodopsin2 (ChR2) or archaeorhodopsin (ArchT), respectively. Adeno-associated virus (AAV)-ChR2-EYFP or AAV-ArchT-GFP were bilaterally injected into TRN in PV-Cre mice, implanted with optical fibers targeting TRN, and instrumented to record sleep. ChR2 excitation of PV TRN neurons at 10Hz (n=5) elicited both a significant increase of cortical EEG power at the stimulation frequency, and consistently produced cortical EEG spindles when the mouse was in NREM sleep. Concomitantly, there was an increase (~30%) in NREM sleep (n=2) while wake decreased. ArchT inhibition of TRN PV neurons blocked the ongoing spontaneous trains of spindles for 4s ($p<0.0001$; vs. no laser); and increased wake time (28%) (n=4). ArchT inhibition of TRN PV neurons also enhanced the cortical response to 40 Hz auditory stimulation, suggesting an enhancement of sensory transmission. To test if the BF-to-TRN pathway modulates spindles, we stimulated the BF PV terminals in the TRN with laser light after injecting AAV-ChR2-EYFP into BF and studied spindle modulation. ChR2 BF PV terminal stimulation (n=1 thus far) in TRN blocked 90% of ongoing spontaneous spindles for >15 sec (vs. no laser). An increase in wake (22%), compared to no stimulation was also observed in this mouse. Based on the results, we conclude TRN PV neurons generate cortical spindles and influence NREM sleep. The BF-to-TRN pathway modulates spindles with the consequence that spindles are inhibited when during BF PV neurons are active. These mechanistic insights are

ultimately important for pharmacological target development for spindle deficits in Sz that are based on TRN or BF PV neuronal abnormalities.

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Poster

814. Sleep: Regulators

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 814.19/Y37

Topic: E.08. Biological Rhythms and Sleep

Support: DARPA W911NF1010066

Title: Phenotype associations in a battery of psychiatric assays, stress measurements, and sleep traits in an F2 mouse population

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Abstract: >Psychiatric disorders in humans are known to be associated with stress susceptibility and sleep disturbances, though the nature of these connections are not clear. We wished to see how these traits are related in mice, both phenotypically and genetically. (C57BL/6 x A/J) F2 mice (N=338) were tested in a multi-week battery of behavioral and physiological assays, including but not limited to elevated plus maze, open field arena, forced swim test, fear conditioning, glucose tolerance test, restraint stress, corticosterone measurements, immunological measurements, and telomerase activity. We then implanted the mice with head electrodes and recorded electroencephalogram signals in order to quantify their sleep during baseline conditions as well as during recovery from sleep deprivation and restraint stress. Although correlations between phenotypes were sparser than expected, many interesting associations were discovered. We used factor analysis and clustering to categorize similar phenotypes into groups and discover hidden structure in the data. Predictable associations were seen, such as between body weight and glucose, between various anxiety tests, and between REM sleep traits and retention of fear conditioning. Many more unexpected associations were also observed, such as between circadian timing of sleep and glucose tolerance, elevated plus maze performance and REM sleep after restraint, and corticosterone and sleep fragmentation.

The relationships found in this phenotypic dataset will generate many interesting hypotheses that spur further investigation. Acknowledgements: This work was supported by The Defense Advanced Research Projects Agency (government contract/grant number W911NF1010066). The views, opinions, and/or findings contained in this article are those of the author and should not be interpreted as representing the official views or policies, either expressed or implied, of the Defense Advanced Research Projects Agency or the Department of Defense.

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Poster

814. Sleep: Regulators

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Topic: E.08. Biological Rhythms and Sleep

Title: Complex sleep architecture is common to parrots, songbirds, and mammals

Authors: *S. CANAVAN, D. MARGOLIASH;
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Abstract: Avian sleep reportedly lacks several traits of mammalian sleep, including significant amounts of rapid eye movement sleep (REM) and slow wave sleep (SWS), and an ultradian pattern that governs sleep stage proportions across the sleep period. Although such traits have recently been identified in multiple songbird (oscine passerine) species, reptilian sleep possesses none of these traits, suggesting convergent evolution in mammals and songbirds. To determine whether these sleep traits also appear in non-songbird lineages of birds, we investigated sleep architecture in the budgerigar (Melopscittacus undulatus). Five adult budgerigars (3 female, 2 male) were implanted with electrodes to measure the electroencephalogram (EEG) and electrooculogram (EOG). Behavioral signs of sleep were monitored via continuous infrared video recording. Sleep data were analyzed by expert manual scoring and by a k-means clustering algorithm previously used to classify sleep stages in zebra finches and starlings. Sleep was classified into 3 states: a REM-like state, a SWS-like state, and a non-REM intermediate sleep state. Surprisingly, we found that budgerigars spent significant time in REM-like sleep. They also exhibited an ultradian pattern of decreasing SWS and increasing REM. Like other birds, budgerigars lacked both sleep spindles during non-REM and consistent muscle atonia during REM. We confirmed that the pattern of sleep structure in budgerigars is disrupted when birds are

maintained in constant light conditions, as reported in the only prior study of budgerigar sleep. Our results motivate a reinterpretation of the evolution of avian sleep. Recent molecular phylogenetic analysis reveals that parrots and songbirds are sister taxa sharing a single common ancestor. It remains to be determined if other avian taxa exhibit more complex sleep architecture than previously recognized. Such investigations may open a window into what are the mechanisms giving rise to complex sleep architecture, and what attributes were shared through reptiles or arose independently in birds and mammals.

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Poster

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Topic: E.08. Biological Rhythms and Sleep

Support: University of Miami Start Up to Dallman

Title: High glycine prolongs recovery time from anesthesia

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Abstract: Of the estimated sixty thousand individuals who undergo general anesthesia daily, thousands experience significant delays as they emerge from the anesthetized state (Aldrete and Kroulik, 1970; Philip et al., 1996). Such delayed emergence from anesthesia was recently linked elevated nervous system glycine by a case study of a three-year-old girl with an inherited disorder, Glycine Encephalopathy (GE) (Liu and Fan, 2006). The anesthesiologists hypothesized that delayed emergence in their patient was caused by elevated glycine. To test this idea, we used zebrafish glial glycine transporter (GlyT1) mutants as a model. Like individuals with GE, GlyT1 mutants have elevated nervous system glycine, and, like the anesthetized GE patient, we found that GlyT1 mutants show delayed emergence from anesthesia. Despite this delayed emergence, GlyT1 mutants exhibit a normal dose/response curve for anesthesia-induced sedation, indicating elevated glycine specifically impacts emergence. We hypothesized that high nervous system glycine in GE and GlyT1 mutants might disrupt arousal pathways known to be required

specifically for timely emergence from anesthesia. Consistent with this idea, we were able to overcome delayed emergence from anesthesia in GlyT1 mutants either by reducing glycine, blocking $GABA_A$ receptors or by stimulating dopaminergic arousal pathways. Moreover, we show that in addition to delaying emergence from anesthesia, high glycine disrupts state transitions more generally, indicating that measurements of arousal state prior to anesthesia might be able to predict complications during emergence from anesthesia. Our results support a mechanism whereby elevated glycine inhibits brain arousal pathway to delay emergence from anesthesia.

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Poster

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Title: Improved Sleep related Gene Ontologies through analysis of KOMP2 sleep phenotyping data and gene expression studies

Authors: *S. JOSHI[1], M. SETHI[1], M. STRIZ[1], N. COLE[4], J. RYAN[4], M. E. LHAMON[5], A. AGARWAL[5], S. J. SUKOFF RIZZO[4], J. M. DENEGRE[4], R. E. BRAUN[4], D. W. FARDO[2], K. D. DONOHUE[3], E. J. CHESLER[4], K. L. SVENSON[4], B. F. O'HARA[1];
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Abstract: A nearly random gene ontology (GO) for sleep-related genes and lack of a dedicated database containing a comprehensive list of these genes and their function presents a hurdle for sleep researchers. Increased data from sleep phenotyping studies in mouse and other species, genetic crosses, and gene expression databases can all help improve this situation. Here, we present our own sleep data from the large scale phenotyping program at The Jackson Laboratory (JAX), and then utilize publically available gene expression data to potentially strengthen and

help understand the best gene candidates for influencing sleep traits. The original knockout mouse project (KOMP) was a worldwide collaborative effort to produce embryonic stem (ES) cell lines with one of mouse's 21,000 protein coding genes knocked out. The objective of KOMP2 is to phenotype as many as of these lines as feasible, with each mouse studied over a ten week period (www.mousephenotype.org). The phenotyping for sleep behavior is done using our non-invasive Piezo system for mouse activity monitoring. Thus far, we have recorded sleep behavior in more than 1500 mice representing 150 knockout lines and over 1000 control mice. We have compared control and KO mice using multivariate statistical approaches to identify genes that exhibit significant effects on sleep variables from Piezo data. Using these statistical approaches, we have been able to identify significant genes affecting sleep specifically during daytime and/or night. Sleep is governed by both circadian and homeostatic processes. While the circadian process is dependent on time of day, the homeostatic process is affected by previous sleep. To study if the genes identified from KOMP2 data are associated with circadian or homeostatic sleep processes, we are using gene expression data from NCBI GEO (National Center for Biotechnology Information - Gene Expression Omnibus) database. Using a pattern matching approach, gene expression patterns of previously identified circadian and sleep related genes are matched with those of candidate genes from KOMP2. While important sleep-related genes will not necessarily change mRNA levels AND sleep phenotypes, those that do may be especially good candidates to pursue further. The use of gene expression and KOMP2 data for improved lists of sleep related genes should represent a substantial improvement over the existing list of genes returned using the query "sleep" or other similar terms in gene ontology database, and should be useful to help identify key players and key pathways in sleep regulation, sleep function, and both direct and indirect influences on sleep behavior.

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Poster

814. Sleep: Regulators

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Topic: E.08. Biological Rhythms and Sleep

Support: University of Zurich–Clinical Research Priority Program (CRPP) Sleep and Health.

Title: Slow wave activity increase after acute sleep deprivation and after chronic sleep restriction

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Abstract: **Introduction** Increased slow wave activity (SWA), i.e. spectral power in the 1-4.5 Hz range in the sleep electroencephalography (EEG), is a well-established marker of sleep pressure. The impact of sleep loss on neurobehavioral functioning differs between individuals, with some showing more impairments than others. This individual vulnerability is preserved across different paradigms of sleep loss, e.g. when comparing acute sleep deprivation (aSD) and chronic sleep restriction (cSR). Up to date, it is not known if increased SWA reflects an individual vulnerability to sleep loss too. Thus, we aimed at directly comparing the amount of SWA increase after aSD and cSR in the same subjects. **Methods** Nine male subjects underwent 40 hours of aSD and 7 nights of cSR (5h instead of 8h sleep/night) in a counterbalanced way. Sleep was recorded during a baseline night prior to any sleep loss, after aSD, and after 7 nights of cSR, using high-density EEG (128 electrodes). We compared the increase in SWA (power density in the 1.25-4.5 Hz range) during the first sleep cycle of the recovery nights after aSD and cSR relative to the baseline night. The relative increase of SWA in individual electrodes was averaged over clusters of electrodes corresponding either to the frontal, parietal, occipital or temporal lobe. Comparisons were performed by paired t-test. To investigate the relationship between the relative increase in SWA over different brain areas after aSD and cSR, we calculated partial correlations controlling for baseline levels of SWA. **Results** The increase of SWA observed after aSD was higher in all areas compared to cSR (smallest difference in the parietal cluster +32.4 ± 12.5% [mean ± SD], $p<0.001$, largest difference in the occipital cluster +43.2 ± 14.2%, $p<0.001$). The increase in SWA after aSD and after cSR was significantly correlated in all areas. The correlation coefficient ranged from $r = 0.78$ ($p<0.05$) for the frontal lobe to $r = 0.90$ ($p<0.01$) for the temporal lobe. **Conclusions** Despite large differences in the increase of SWA after aSD compared to cSR, the relative SWA increase over different brain regions after the two kinds of sleep loss is highly correlated in the same subjects. These results imply that the SWA increase after sleep loss might reflect an individual's vulnerability to sleep loss. Notably, this relationship is not merely a result of differences in baseline levels. Further

analysis looking into potential regional differences more closely and relating the vulnerability to sleep loss as measured by SWA to neurobehavioral impairments, might contribute to the understanding of the similarities and dissimilarities between the consequences of acute and chronic sleep loss.

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Poster

814. Sleep: Regulators

Location: Hall A

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Program#/Poster#: 814.24/Y42

Topic: E.08. Biological Rhythms and Sleep

Title: Circadian regulation of perineuronal net composition

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Abstract: Background: Perineuronal Nets (PNNs), extracellular matrix structures that envelop subpopulations of neurons and restrict synaptic plasticity, were long thought to be stable, cartilage-like structures. Recent studies however suggest that PNN composition is modified during learning tasks, possibly allowing for formation of new synapses in response to environmental stimuli. New synapses are believed to undergo strengthening during sleep, a process termed ‘memory consolidation’. We tested the hypothesis that PNNs are regulated in a circadian manner, possibly allowing for increased plasticity during active periods and contributing to strengthening of new synapses during sleep. Methods: Total numbers and numerical densities of PNNs labeled with wisteria floribunda agglutinin lectin (WFA), or with the antibody cat-301 directed against the aggrecan core protein, were quantified in the amygdala and reticular nucleus of the thalamus (RTN) in a cohort of postmortem brain samples from normal human subjects (12-15 subjects) and plotted by time of death for each subject. Glycomics analysis was carried out using mass spectrometry on free-floating sections from the human amygdala and RTN to quantify specific sulfated chondroitin sulfate (CS) disaccharides. In addition, WFA and cat-301 were used to quantify PNNs in a cohort of wild type male 129sv mice sacrificed every 4 hours across the 24 hour cycle in the amygdala, thalamus, hippocampus, and prefrontal cortex. Results: We observed a ‘rhythmic-like’ relationship of WFA labeled PNNs

in the human amygdala and RTN. In addition, mass spectrometry analysis of CS disaccharides in the RTN revealed a rhythmic-like relationship of non-sulfated CS, as well as the 4S to 6S sulfation ratio, with time of death. In comparison, aggrecan immunoreactive (IR) PNNs in the human amygdala did not show a 'rhythmic-like' relationship with time of death. In mice, we observed a similar rhythmic distribution of WFA labeled PNNs in the RTN and in the lateral and basolateral amygdala nuclei. Quantification of WFA labeled PNNs in the hippocampus and prefrontal cortex, and of aggrecan-IR PNNs in mice, is in progress. Conclusion: Our data suggest that PNN CS composition varies in a circadian manner while the core protein levels do not change. Rhythmic modification of PNNs may contribute to circadian regulation of neuronal firing properties, increased plasticity during active periods, and memory consolidation during sleep.

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Poster

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5T32HL007901-17 to BB

Title: Is schizophrenia associated with a general impairment in sleep-dependent memory consolidation?

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Abstract: Learning and memory impairments are a core feature of schizophrenia (SZ). While sleep promotes memory consolidation in healthy adults, patients with SZ have deficits in sleep-

dependent consolidation of motor procedural memory that are associated with reduced sleep spindle activity. Here we investigate whether this deficit generalizes to other types of memory. We predicted that patients would be impaired in sleep-dependent consolidation of memories that are mediated by spindles. Schizophrenia patients (n=17) and demographically-matched healthy controls (HC, n=14) were trained on three tasks: a declarative word-pair learning task, a statistical learning paradigm that tests recognition of regularities in tone sequences, and a visual discrimination task that involves procedural learning. Performance was tested 24 hrs later after a night of sleep. Relative to controls, SZ patients showed a non-significantly greater decrement in word-pair recall (13.5% decrease from training in SZ; 4.7% in HC; $t(30) = 1.4$, $p = .16$). For the statistical learning task, HC showed a 5.9% post-sleep improvement in correctly identified tone sequences while patients showed, a 1% decrement ($t(25) = 1.5$, $p = .14$). In contrast, patients showed greater performance improvement on the visual discrimination task than HC (SZ: 19%, HC: 9%; $t(23) = 1.4$, $p = .18$). Results provide preliminary support for the hypothesis that types of memory mediated by spindles (i.e. declarative memory and abstraction of statistical regularities) are impaired in schizophrenia. Future plans include increasing the sample size to determine whether SZ is associated with a reliable pattern of sleep-dependent consolidation deficits that correspond to spindles, and determining whether memory deficits are related to the functional and structural integrity of thalamocortical circuits that mediate spindles using diffusion tensor imaging and resting-state functional connectivity MRI.

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Poster

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Topic: E.08. Biological Rhythms and Sleep

Support: NSF Grant BCS-0963581

Title: Sleep leads to enhanced amygdala connectivity during retrieval of emotional items and the neutral contexts with which they were previously studied

Authors: *K. A. BENNION[1], J. D. PAYNE[2], E. A. KENSINGER[1];
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Abstract: INTRODUCTION: Although prior research has shown that sleep selectively consolidates emotional memory, as well as enhances connectivity among limbic regions during emotional memory retrieval (Payne & Kensinger, 2011), this work has typically utilized emotional cues. What is unknown is whether sleep affects retrieval processes when the retrieval cue is void of the emotionally salient component of a stimulus (i.e., the retrieval of a neutral background previously studied with emotional content), and also how sleep during consolidation affects these processes. The present study investigates amygdala connectivity following sleep versus wake during retrieval of 1) emotional items and 2) the neutral backgrounds they were studied with, the latter determining if residual effects of emotion on limbic connectivity persist even once the emotional cue is no longer present. METHOD: Participants encoded scenes composed of a negative or neutral item on a neutral background either in the morning (preceding 12 hours awake; Wake group) or evening (preceding 12 hours including a night of sleep; Sleep group). At retrieval, during fMRI, participants viewed the items and backgrounds separately, distinguishing new items and backgrounds from those previously studied. RESULTS AND DISCUSSION: Following Sleep (relative to Wake), there was enhanced connectivity between an amygdala seed region (-24 -6 -22) and several regions, including the insula, parahippocampal gyrus, precuneus, posterior cingulate, middle frontal gyrus, and superior and middle temporal gyrus, during the retrieval of negative versus neutral items. There was also some evidence of sleep enhancing amygdala connectivity during retrieval of neutral backgrounds studied with emotional content, particularly with the medial prefrontal gyrus and three clusters within the precentral gyrus. Conversely, there were no regions that exhibited greater connectivity with the amygdala following Wake greater than Sleep, either for emotional items or their neutral backgrounds. This provides further evidence for sleep leading to profound changes within the emotional memory retrieval network, and demonstrates for the first time that residual emotion effects may be reflected in amygdala-frontal lobe connectivity, following sleep but not wake.

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Poster

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Topic: E.08. Biological Rhythms and Sleep

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Title: Identification of sleep patterns in dominant and submissive crayfish

Authors: M. OSORIO-PALACIOS[1], *K. MENDOZA-ANGELES[2], G. ROLDAN[1], J. HERNÁNDEZ-FALCÓN[1];
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Abstract: Different biological models used until now show that sleep is essential not only to have a good quality of life, but for the maintenance of life itself. The crayfish is an invertebrate with a 'simple' brain in which many functions have been studied. Previously it has been demonstrated that crayfish sleep fulfills behavioral and electrophysiological criteria defined for vertebrates. When crayfish are in social interaction, they establish a hierarchical order of dominance-submission. Preliminary results, obtained from behavioral observations, indicate that dominant and submissive animals have different sleep patterns. It has not been determined whether sleep patterns determine the role that a given crayfish will play in the hierarchical order, or if hierarchical scale determines the sleep pattern of crayfish of a given triad. The aim of this work was to study the behavioral and electrophysiological sleep patterns of adult isolated crayfish Procambarus clarkii and the effects induced by the establishment of a dominance-submission social relationship. We used triads of male crayfish in intermolt, synchronized to light-dark cycles 12:12. Animal's weight and size differ in less than 10%. We performed behavioral recordings of crayfish triads placed in individual aquaria during 24 continuous hours. Then, we placed the animals in a common aquarium during 48 hours. To analyze the recordings we quantify the following variables: a) total sleep time, b) number of position transitions, and c) length of sleep interval. Each crayfish showed a different sleep pattern during the isolation period. The would-be dominant animal had the greater total sleep time, fewer position transitions, and the longest duration of sleep intervals. The submissive crayfish 1 showed shorter sleep duration periods and a high number of transition position. In comparison, the submissive crayfish 2 had the shorter total sleep time. When animals were in social interaction, the dominant crayfish decreased its total sleep time and displayed fewer transitions in position. Submissive animals further reduced their total sleep time; nonetheless, submissive crayfish 1 increased significantly the number of transitions in position. These findings suggest that dominance is associated with a great ability to adapt even in complex functions as sleep.

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Poster

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Topic: E.08. Biological Rhythms and Sleep

Support: Institute for Scholarship in the Liberal Arts Founders' and Directors' 30th Anniversary Research Award

Title: Sleep benefits memory to complete goal-relevant behavior

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Abstract: Prospective memory (PM), or the ability to plan and spontaneously remember to execute activities in the future, is a vital skill that healthy individuals utilize every day without even knowing it. Recent evidence demonstrates that sleep enhances PM abilities in the context of a semantic categorization task (Scullin and McDaniel, 2010). The goal of the present study was to determine if sleep's benefit to prospective memory would be generalized across a variety of tasks. Participants were divided into 4 groups: morning short-delay (n=16), evening short-delay (n=16), morning long-delay (wake group, n=30), and evening long-delay (sleep group, n=30). Each group completed two sessions. Morning participants arrived to the lab for session one at 9am and evening participants at 9pm. Session one began with a battery of cognitive tests including three ongoing tasks: living/nonliving decision, lexical decision, and semantic categorization. After completion of the final ongoing task, a PM instruction to be carried out during the second session was given (i.e., hit "q" whenever "table" or "horse" appears), followed by a 20 min distracter task. Following this task, short-delay groups immediately completed the second session, while the wake and sleep groups were dismissed for a 12-hour period spanning daytime wakefulness or nocturnal sleep, respectively, before returning for the second session. The second session included another round of the ongoing tasks and a test of prospective memory for the critical words. Results showed that there was no main effect of task type, indicating that performance was similar across all three tasks. Because the morning and evening short-delay groups did not differ in performance [$t(30) = 1.3$, $p=0.2$], these groups were collapsed into a single short-delay group. Critically, the wake group showed significant PM deterioration compared to the short-delay group [$t(60)=3.94$, $p < 0.0001$], while the sleep group did not significantly differ from the short-delay groups. These results suggest that sleep protects the ability to successfully perform future actions, while wakefulness degrades this ability . This study not only replicates a previous report indicating that sleep benefits prospective memory performance, but also extends it by suggesting that this effect is not limited to a certain test context, and can be generalized across different testing modalities. During sleep, our daily goals may be reactivated and rehearsed leading to a better chance of remembering to execute them at the appropriate time.

Disclosures: T. Cunningham: None. **A.M. Chambers:** None. **J.D. Payne:** None.

Poster

815. Sleep: Systems

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Topic: E.08. Biological Rhythms and Sleep

Support: ONR N00014-13-1-0672

NIH R01 MH099645

NIH R01 EB009282

NINDS RO1 NS062092

Title: Generation of spontaneous EEG rhythms across cortical layers in humans

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Abstract: Cortical rhythms are a central aspect of brain activity and have been implicated in information transfer, network dynamics and synaptic plasticity. Though various recording modalities have been used in humans and animal models to correlate rhythms with cortical areas and states, little has been done to shed light on which cortical layers generate which frequency bands. To investigate this, we used laminar electrodes with 40 micron diameters and 150 microns between contact centers implanted in the grey matter of patients with medically intractable epilepsy to examine how the power spectrum of the spontaneous LFP changes across cortical layers. Superficial layers were responsible for almost all of the power between 1-6 hz. After this, the dominant frequency band gradually increased with cortical depth. From about 1-20 hz, a positive relationship between cortical depth and frequency was found across patient, state (wakefulness or non-REM sleep) and cortical area. This general principle might reflect the longer timescales needed to integrate inputs from distant cortical areas, suggesting that a given column’s information processing becomes increasingly local with depth. This is consonant with the prevalence of cortico-cortical connectivity in superficial layers. Complementing these findings, Shannon’s entropy was found to decrease with cortical depth, perhaps indicative of a

higher degree of informational complexity associated with cortico-cortical processing. Coherence and mutual information were also used to assess functional connectivity between layers. Although significant connectivity was found between and within supragranular and infragranular cortical layers, a putative layer IV exhibited little coherence/mutual information with other layers. This suggests that layer IV participates in a different kind of informational processing than other cortical layers, possibly reflecting its role as a recipient of topographic feed-forward input whereas superficial and deep cortex might be co-modulated by coherent afferents. These differences may also be explained by thalamocortical matrix/core afferents, the former synapsing diffusely on superficial and deep cortex driving coherent activity, and the latter topographically in granular cortex. Although these results are significant for understanding network processing, they also have important implications for the interpretation of ECOG, EEG and MEG. Superficial LFP was found to have large broadband power, suggesting that the oscillatory activity measured on the scalp/cortical surface is dominated by supragranular activity, and by extension cortico-cortical, cognitive processing.

Disclosures: **M. Halgren:** None. **I. Ulbert:** None. **J. Madsen:** None. **W.K. Doyle:** None. **E. Halgren:** None. **S.S. Cash:** None.

Poster

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Topic: E.08. Biological Rhythms and Sleep

Support: NIH (R01AG046646)

ONR (MURI: N000141310672)

Title: Phase-amplitude coupling of sleep spindles and slow oscillations improves verbal memory

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Abstract: Prior studies have shown that boosting non-rapid eye movement (NREM) sleep spindles (12-15Hz) (Mednick et al. 2013) and slow oscillations (SOs, 0.5-1Hz) (Marshall et al. 2006) in a targeted manner selectively enhances declarative memory, suggesting a causal role for each oscillatory band independently. However, the functional consequence for memory of coupling between spindles and SOs, when they co-occur, is not known. Here, we use signal

processing techniques to address this question. Thirty subjects were tested in two drug conditions (zolpidem and placebo) on a verbal memory task. Recorded EEG during stage 2 sleep was first filtered (0.5-1Hz). Spindle windows were set to 1-sec before and 1-sec after spindle markers. Spindle/SO complex were identified when the maximum amplitude envelope of the signal crossed a threshold 2-sec before a spindle. The phase of SOs at the peak of the spindle amplitude envelope was calculated within the spindle window. We also calculated the unwrapped phase change of SOs in the interval between the peaks of SO and spindle amplitude envelopes in order to consider phase across cycles, as well as the normalized modulation index. We found that correlation of the mean of the actual phase of SO at the peak of the spindle amplitude envelope with performance improvement in the zolpidem condition was higher ($r=-.446$; $p=.017$) than that in the placebo condition ($r=-.369$; $p=.057$). These findings indicate that tighter coupling between SO and spindles increased memory consolidation in both groups, but that zolpidem intensified this effect. These data also suggest a preferred SO phase for the occurrence of spindles events that resulted in better memory consolidation. The unwrapped phase change of the SOs was significantly correlated with performance improvement in zolpidem condition ($r=.597$; $p<.001$) but not in placebo condition ($r=.111$; $p=.579$). Moreover, the normalized modulation index for spindle/SO complexes was significantly higher in the zolpidem condition compared to the placebo condition ($p=.004$) indicating stronger coupling between SOs and spindles in zolpidem condition. Our study revealed that memory consolidation critically depends on the tight temporal coupling of spindle and SO events. Occurrence of the maximum spindle amplitude at a certain phase of SO predicted performance improvement across all subjects in both groups. Pharmacological intervention with zolpidem may have increased the magnitude of this effect by increasing the modulation index. These findings suggest the existence of a preferred phase of SO, in which the spindle maximum should occur for optimized consolidation.

Disclosures: **M. Niknazar:** None. **G. Prashanth:** None. **M. Bazhenov:** None. **S.C. Mednick:** None.

Poster

815. Sleep: Systems

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Topic: E.08. Biological Rhythms and Sleep

Support: Hungarian Scientific Research Fund OTKA NF101773

Hungarian Brain Research Program KTIA_NAP_13-2014-0016

Title: Cortical layer 6. modulates spindle generation in thalamus

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Abstract: Sleep spindles are generated by the interplay of excitatory thalamocortical (TC) and inhibitory thalamic reticular (nRT) neurons. Stimulation of nRT cells or axon terminals can elicit spindles in a state dependent fashion. The third component of the network, layer 6. of the cortex (L6) provides excitatory feedback to both cell types, however its role in spindle generation is unclear. We recorded thalamic multiunit activity in urethane anaesthetized NTSR1-ChR mice, a strain expressing channelrhodospin in L6 corticothalamic cells selectively. Brief, pulse-like light stimuli to L6 terminals elicited spindles in a fashion similar to direct nRT activation. Namely, no spindles could be evoked during deeply synchronized and desynchronized network states, only during light synchronization, a state analogous to stage 2. sleep, in which spontaneous spindles also appear. Tonic L6 stimulation, on the other hand, elicited a progressively increasing thalamic multiunit activity, which ended in a complete cessation of firing for several seconds, possibly through a depolarization block. We assume that the former effect is mediated by direct L6 activation of nRT, while the latter through TC cells.

Disclosures: **P. Bartho:** None. **F. Matyas:** None. **M. Csernai:** None.

Poster

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Topic: E.08. Biological Rhythms and Sleep

Support: Swiss Natl Sci Found 146244

Etat de Vaud

Title: Infra-slow neural and cardiac fluctuations predict behavioral arousability during mouse NREM sleep

Authors: S. LECCI[1], L. M. J. FERNANDEZ[1], R. D. WIMMER[2], J.-Y. CHATTON[1], *A. LUTHI[1];
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Abstract: Environmental noise at night disrupts sleep and adversely affects general health by causing daytime sleepiness and increasing cardiovascular risk factors. This calls for a profiling of sleep in terms of fragility to acoustic disturbance and in association with cardiovascular activity. Electrophysiological and imaging studies in humans and animals show that thalamocortical sleep rhythms cause substantial sensory response variability. Nevertheless, the tell-tale signs that determine whether or not noise causes behavioral arousal remain incompletely understood. Here we show that noise-induced arousal is specifically predicted during mouse non-rapid-eye-movement sleep by an infra-slow fluctuation (periodicity ~45 s) in the power of sleep spindles, a 10-15 Hz electroencephalographic rhythm implied in sleep's beneficial actions on memory formation, which is phase-locked to slow components of heart rate variability. By choosing an acoustic stimulus such that mice wake up or sleep through noise at comparable rates, we discovered that, prior to noise onset, sleep spindle power peaked when an arousal followed. Conversely, sleep-through was preceded by a trough in spindle power, concurrent with augmented heart rate fluctuations. Varying arousability hence arises from joint central autonomous and sleep-wake control mechanisms, going beyond traditional views of thalamocortical sensory gating. Infra-slow fluctuations occurred in sensory and associational cortical areas and were suppressed by zolpidem, a widely used hypnotic drug, substantiating their role as sleep fragility markers. Together, we show for the first time that arousability during mammalian sleep fluctuates constantly due to a specific brain-heart crosstalk. The coordination between a salient sleep rhythm and an index for cardiac health bears the potential for assessing the pathophysiological links between sleep disorders, cognitive deficits, and cardiovascular disturbance.

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Poster

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Topic: E.08. Biological Rhythms and Sleep

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Swartz Foundation

Howard Hughes Medical Institute

Title: Nonlinear dynamical features for improving computational sleep models using Delay Differential Analysis

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Abstract: Cortical network models based on ionic mechanisms have many parameters that must be chosen to match cortical recordings. One measure is comparison of the local field potentials generated by simulations of the model with electrocephalogram (EEG). Here, we use delay differential analysis (DDA), which is a time domain classification framework based on embedding theory in nonlinear dynamics to make the comparison. An embedding reveals the nonlinear invariant properties of an unknown dynamical system (here the brain) from a single time series (here EEG data). The embedding in DDA serves then as a low-dimensional nonlinear functional basis onto which the data are mapped. Since the basis is built on the dynamical structure of the data, preprocessing of the data (such as filtering) is not necessary. DDA yields a low number of features (around 4), far fewer than traditional spectral techniques. This greatly reduces the risk of overfitting. A model that was trained on a single EEG channel from one subject can be applied to a wide range of data from different subjects, channels, and recording systems. In this project, we varied the network's thalamocortical fan-out to simulate networks with different levels of connectivities. Then, we apply DDA to construct a set of non-linear features for the real human sleep EEG data and each network simulation. Finally, the cross correlation between each network simulation and the real sleep data is computed. Our results show that within the connection range we simulated, networks with medium levels of fan-out rate have the highest correlation with real sleep data. This implies that there is an optimum level of connection between the thalamus and the cortex. A too narrow or too broad fanout will disrupt the simulation dynamic from that of real sleep. (Lainscsek, C. Sejnowski, T. J. Delay Differential Analysis of Time Series, Neural Computation, 27, 594-614, 2015)

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Poster

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Support: Dixon Translational Research Grant

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NSF GRFP DGE 1324585

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Title: Using Acoustic stimulation to increase slow-wave activity and improve memory in older adults

Authors: *P. A. PAPALAMBROS[1], G. SANTOSTASI[1], R. G. MALKANI[1], S. WEINTRAUB[2], K. A. PALLER[3], P. C. ZEE[1];
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Abstract: Age-related decrease in the amount of slow-wave sleep has been postulated to play a role in impaired cognitive and metabolic function. Acoustic stimulation during sleep has been shown to increase slow-wave activity (SWA) in young adults but has not been examined in older adults. The aim of this study is to examine the ability of acoustic stimulation to increase SWA in adults ≥50 years old. Twelve cognitively healthy adults (age 68.9 ±9 years, 2 male) completed one night of acoustic stimulation and one night of sham stimulation. During sleep, an adaptive phase-locked loop (PLL) algorithm was used to lock on to endogenous slow waves measured in midline frontopolar electroencephalographic recordings in real time. Acoustic stimuli were delivered when the PLL system predicted the positive upstate of the slow wave. Stimuli consisted of pulses of pink (1/f) noise lasting 50 ms with an inter-tone interval of approximately 1 s, depending on the individual's slow oscillations. Tones occurred in blocks of 5 pulses ("ON blocks") followed by a refractory period of equal length ("OFF blocks"). Participants completed a declarative memory 88-word pair test before and after sleep. Power spectral analysis was used to identify power in the slow oscillation delta frequency band (slow delta: 0.8Hz-2.1Hz). Wilcoxon signed-rank test was used to evaluate differences in power within and between stimulation and sham nights. Memory scores are a subtraction of the raw evening score from the raw morning score to give a change in memory. During the stimulation night, there was a 58.7% increase in slow delta during the ON blocks compared to OFF blocks ($p=0.015$). Slow delta during ON blocks during the stimulation night was 61.1% higher when compared to ON blocks in the sham night ($p=0.018$). On average, participants recalled 5 more words when tested the morning following a sham night, and 8.8 words the morning following a stimulation night. This reflects a relative improvement of 3.8 additional words with auditory stimulation. Acoustic stimulation during sleep can enhance SWA and has the potential to improve sleep quality and

memory in middle age and older adults. Acoustic stimulation may be a drug free alternative to improving memory in those with cognitive decline.

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Poster

815. Sleep: Systems

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Topic: E.08. Biological Rhythms and Sleep

Support: Yale-NUS College Start-up Grant R-607-264-057-121

Title: Weighing in on sleep: Exploring the relation between maternal sleep patterns during pregnancy and subsequent weight gain of the child

Authors: K. VIJAYAKUMAR[1], B. LOW[1], J. J. GOOLEY[2], Y. S. LEE[3], F. YAP[4], M. F. F. CHONG[5], B. BROEKMAN[5], A. RIFKIN-GRABOI[5], M. MEANEY[5], P. GLUCKMAN[5], K. KWEK[4], Y. S. CHONG[3], *J. C. LIU[6];
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Abstract: A large body of epidemiological studies suggests that sleep deprivation is a risk factor for illness and for all-cause mortality. While within-person effects have been catalogued extensively, there has been recent interest in possible transgenerational effects of sleep deprivation. Results from rodent studies suggest that maternal sleep deprivation during pregnancy may have profound effects on the weight and food preferences of the offspring. In humans, a cohort study likewise found that maternal sleep deprivation was a risk factor for low birth weight. In this study, we sought to extend these findings by exploring how maternal sleep patterns would relate to the weight status of a child over a longer period of observation. 545 female participants were recruited during their pregnancy as part of the "Growing Up in Singapore Towards healthy Outcomes" study (GUSTO), an ongoing longitudinal study where both mothers and their children are observed from gestation until the child is seven years of age. As a measure of maternal sleep, mothers completed the Pittsburgh Sleep Quality Index (PSQI) between the 26th and 28th week of pregnancy. This is a standardised self-reported measure assessing sleep duration and quality during the past month. For our analyses, we focused on a

single question requiring participants to estimate the hours of sleep they obtain in an average night. This was correlated with the child's body mass index (BMI) at three years of age. We found a significant negative correlation between maternal sleep duration and the child's BMI. Namely, decreased habitual sleep during pregnancy was associated with an increased risk for offspring weight gain at three years of age. This is consistent with prior rodent studies suggesting transgenerational effects of sleep deprivation. However, we note also that our observed correlation was weak, raising the possibility of mediating variables underlying this relationship.

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Poster

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Topic: E.08. Biological Rhythms and Sleep

Support: BUMED #307

ONR-W1AE

Title: Spectral analysis of sleep EEG reveals new deep sleep stage with dominant frequencies below 1 Hz

Authors: *J. A. ONTON[1,2], V. VIJAYAN[3], C. PARK[4], S. KIM[5], T. P. COLEMAN[5]; [1]Warfighter Performance Dept 162, Warfighter Performance, San Diego, CA; [2]Inst. for Neural Computation, Univ. of CA San Diego, La Jolla, CA; [3]Natera, Inc, San Carlos, CA; [4]Dept. of Computer Engin., Kwangwoon Univ., Seoul, Korea, Republic of; [5]Dept. of Bioengineering, Univ. CA San Diego, La Jolla, CA

Abstract: Traditionally, sleep EEG is interpreted by the trained eye of a sleep technician who can evaluate the EEG and other available measures to determine the sleep stage during each 30 second stretch of time. While this approach can produce reliable estimates of sleep architecture, it is extremely time-consuming and subjective and lacks the possibility of appreciating the spectral complexity of the sleep signal and how this complexity is embedded in the full sleep record. In this study, 40 un-medicated, self-reported normal sleepers, with no problems falling or staying asleep, wore a 2-channel EEG recording device that captured forehead EEG with

reference to the right mastoid. Subjects were instructed on proper self-application of EEG electrodes so that recordings could occur in subject homes without investigator presence. EEG data were decomposed to reveal spectral power fluctuations over the course of the entire night from 0.1 Hz to 145 Hz for each channel individually and for the forehead-forehead difference channel. Spectral band power was submitted to a customized Hidden Markov Model and Expectation-Maximization algorithm for automatic scoring based on priors derived from the literature and observed spectral qualities of the data. This approach provides a rapid and accurate display of sleep architecture, and a means for quantification of sleep stage durations. Using this technique, we were able to detect distinct stages of deep sleep that are characterized by 1-3 Hz power dominance ('hi deep') and 0.1-1 Hz dominance ('lo deep'), respectively. Presence of lo deep sleep is almost always present in one or more cycles in normal sleepers, while hi deep sleep is less consistently present, but is most common in the first sleep cycle. Preliminary, investigations indicate that the electrodermal response (EDA) is correlated specifically with the lo deep sleep stage and may therefore represent a physiologically distinct and important sleep stage.

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Poster

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National Science Foundation Graduate Research Fellowship

Chateaubriand Fellowship

Title: Distribution, amplitude, incidence, co-occurrence, and propagation of human K-Complexes in focal transcortical recordings

Authors: *R. A. MAK-MCCULLY[1], B. Q. ROSEN[2], M. ROLLAND[2], J. REGIS[3], F. BARTOLOMEI[3], P. CHAUVEL[3], S. S. CASH[4], E. HALGREN[2];
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de Neurosciences des Systemes UMR 1106, APHM (Assistance Publique-Hopitaux de Marseille), Marseille, France; [4]Massachusetts Gen. Hosp. and Harvard Med. Sch., Boston, MA

Abstract: K-complexes are thought to play a key role in sleep homeostasis and memory consolidation. The commonly held view from scalp EEG is that KCs are primarily generated in insular or medial frontal cortex and propagate parietally, whereas ECOG suggests dorsolateral prefrontal generators and an absence of KCs in many areas. We investigated the spatiotemporal relationships of KCs using unambiguously focal bipolar depth electrode recordings in patients with intractable epilepsy. KCs were marked manually on each channel and local generation was confirmed with decreased gamma power. In most cases (76%), KCs occurred in a single location, and rarely (1%) in all locations. However, if automatically-detected KC-like phenomena were included, only 15% occurred in a single location and 27% in all locations. Locally-generated KCs were found in all recorded areas, including cingulate, ventral temporal, and occipital cortices. Surprisingly, KCs vary by >50% in amplitude and incidence across locations, being largest and most frequent in subcallosal and posterior prefrontal areas. When KCs occur on two channels, the order of their peaks is random in 87% of cases. For significant pairs, the only systematic anatomical pattern was a tendency for lateral temporal channels to follow prefrontal. Overall, the anterior-posterior separation of electrode-pairs explained only 2% of the variance in their latencies. These results open a novel view where KCs overall are universal cortical phenomena, but each KC may variably involve small or large cortical regions, and spread in variable directions, allowing flexible and heterogeneous contributions to sleep homeostasis and memory consolidation.

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Poster

815. Sleep: Systems

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NIH R01 EB009282

NIH R01 MH099645

ECOR-MGH Research Scholars Award

Title: Spatiotemporal evolution of the sleep spindle in human neocortex

Authors: *G. PIANTONI[1,2], E. HALGREN[3], S. S. CASH[1,2];
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Abstract: Brain activity is the result of a dynamic interplay between cortical and thalamic neuronal populations and this often takes the shape of an oscillation. A characteristic phenomenon that is generated by the thalamocortical network during sleep is the spindle, a 0.5-2 s long burst of oscillations between 11 and 16 Hz. While animal and computational studies have highlighted the importance of the reciprocal connections between cortex and thalamus, the spatio-temporal properties of the spindle on the cortex remain largely unexplored. We here investigated the evolution of the spindle oscillations over large cortical areas, measured on the human neocortex. Spindles were described by their instantaneous amplitude and phase over neighboring electrodes. We collected recordings from NREM sleep stage 2, using electrocorticography in eight patients undergoing evaluation for intractable epilepsy. Electrodes covered large parts of one hemisphere and were spaced 1 cm apart. The research was approved by the local institutional review board and electrode placement was determined solely by clinical criteria. Based on the instantaneous amplitude in the spindle frequency band for each electrode, we computed the covariance on overlapping 1s long intervals of these time-series. We observed recurring patterns of spatio-temporal organization, which include focal, widespread and global spindling activities. Spindles were more likely to synchronize over multiple cortical areas if they included the lateral prefrontal cortex, a putative pivot of spindle activity. In addition, we observed a drastic phase reset at the beginning of the sleep spindle. We interpret this phase reset as the putative thalamic input to the cortical mantle. The spatial extent of this phenomenon was compatible with the two anatomically defined thalamocortical pathways: the spatially diffuse matrix pathway and the locally selective core pathway. These results highlight the importance of thalamocortical projections in shaping the spindle evolution and define the spatial extent of the functional influence of these projections. These findings will help elucidate the mechanisms underlying spindle generation and the functional role of thalamocortical loops, their possible role in sleep maintenance and memory, and their disruption in neurological disorders.

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Poster

815. Sleep: Systems

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Topic: E.08. Biological Rhythms and Sleep

Title: Sleep deprivation sex-dependently increases myocardial sensitivity to ischemic injury

Authors: ***A. KRIVENKO**[1], M. E. FRY[1], J. D. LAWSON[1], L. E. STONER[1], E. D. EISENMANN[1], B. L. JOHNSON[1], M. L. HEMBREE[1], R. M. ROSE[1], C. J. LOMBARDI[1], M. R. HUNTLEY[1], S. SEELEY[2], A. D. BUI[2], B. R. RORABAUGH[2], P. R. ZOLADZ[1]; [1]Psychology, Sociology, & Criminal Justice, [2]Pharmaceut. & Biomed. Sci., Ohio Northern Univ., Ada, OH

Abstract: Extensive work has shown that sleep deprivation can exert detrimental effects on physiology and behavior. Prolonged sleep deprivation can impair cognitive functions, metabolic processes and cardiovascular activity. The purpose of the present study was to examine the influence of sleep deprivation on myocardial sensitivity to ischemic injury. Male and female Sprague-Dawley rats were exposed to the "flower pot" method of sleep deprivation for 96 consecutive hours. Sleep-deprived rats were placed on a 6.5-cm (diameter) platform in a modified Plexiglas cage that was filled with water to 1 cm below platform level. Control rats were placed on a 13-cm platform in a standard Plexiglas cage that was also filled with water to 1 cm below platform level. Both groups of rats had access to food and water throughout the 96-hr time frame. Following 96 hours in the water-filled cages, rat hearts were isolated and exposed to 20 min ischemia and 2 hr reperfusion on a Langendorff isolated heart system. Sleep deprivation had no effect on pre-ischemic contractile function. However, post-ischemic recovery of contractile function and myocardial infarct size were sex-dependently influenced by sleep deprivation. Specifically, sleep deprivation attenuated post-ischemic recovery of rate pressure product and +dP/dT and resulted in greater post-ischemic diastolic blood pressure in female, but not male, rats. Sleep deprivation also led to greater infarct sizes in females only. These findings are consistent with preclinical and clinical research reporting greater sleep deprivation-induced increases in inflammation, as well as a greater relationship between sleep loss and hypertension, in females.

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Poster

815. Sleep: Systems

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Support: NIH grant-P01 HL095491

Title: CGRP neurons in the external lateral parabrachial nucleus regulate cortical EEG arousal to hypercapnia

Authors: *S. KAUR, J. WANG, D. KROEGER, P. FULLER, C. SAPER;
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Abstract: We have reported that glutamatergic signaling from neurons in the lateral parabrachial region mediates cortical arousal to hypercapnia. This region contains a population of neurons in the external lateral subnucleus (PBel) that express calcitonin gene-related peptide (CGRP), which has extensive forebrain projections and which we hypothesized may be necessary relay for the hypercapnic signal to cause arousal. To test this hypothesis, we employed both opto- and chemogenetic methods to cause acute selective activation or inhibition of the CGRP-PBel neurons by using CGRP-CreER mice. All mice were instrumented for sleep recording and were injected intraperitoneally with tamoxifen (75mg/ kg) to express Cre. In one set of mice (n=5), we bilaterally injected an adeno-associated virus (AAV) containing a Cre-dependent hM3Dq-mCherry transgene targeting PBel, and investigated sleep-wake after Clozapine-N-Oxide (CNO; 0.3mg/kg and 0.1mg/kg, ip) that selectively activated hM3 expressing CGRP-PBel. Activation of CGRP-PBel neurons with CNO (0.3mg/kg) caused a 35% increase in wake ($p<0.05$) during the light phase and significantly suppressed sleep for 2h ($P<0.05$) after CNO injections compared to saline. In another set of mice (n=8), Cre dependent AAV containing Archaerhodopsin from Halorubrum strain TP009 (ArchT) and green fluorescent protein (AAV-FLEX-ArchT-GFP) was injected on one side of the brain targeting the PBel and on other side we deleted the CGRP neurons in the PBel by injecting a Cre dependent virus expressing the diphtheria toxin subunit A (AAV-FLEX-DTA). The ArchT injected side was implanted with optical fiber targeting the PBel. We investigated EEG arousals to 10% CO2 given for 30s every 300s, with and without inhibition of the PBel with a 593nm laser light. Laser light hyperpolarized the ArchT transduced CGRP-PBel neurons, and was on continuously from 20s before every 10% CO2 stimulus until 10s after it. Inhibition of CGRP-PBel neurons increased the average latency to arousal by CO2 by four fold (latency with laser- 69 ± 6 sec; latency without laser- 16 ± 0.6 sec; $P<0.05$), and 49 ± 5% of the trials showed failure to arouse to 30 sec of 10% CO2. Optogenetic inhibition of CGRP neurons did not change their response to acoustic stimuli. Thus, CGRP-PBel neurons mediate cortical EEG arousals to hypercapnia. These neurons project to the lateral hypothalamus, basal forebrain, and central nucleus of amygdala. We propose that these pathways are involved

in mediating the hypercapnic arousals. Current studies are underway to dissect the role of these targets of the CGRP neurons in the PBel in CO2 arousal.

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Poster

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Title: Temporal dynamics of intrinsic activity are reorganized during slow wave sleep

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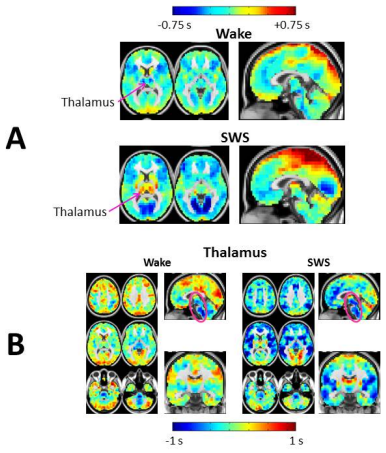
Abstract: Introduction Sleep is essential for normal brain function, but the fundamental functions of sleep remain elusive. Electrophysiological studies have demonstrated multiple, slow (<1 Hz) patterns of propagated activity during slow wave sleep (SWS). Using resting state fMRI (rs-fMRI), we have recently demonstrated multiple patterns of propagated intrinsic activity in normal, awake (W) subjects. Here, we used rs-fMRI to compare and contrast patterns of propagated intrinsic activity in W vs. SWS. Methods 63 nonsleep-deprived subjects were scanned, with simultaneous EEG, in the evening. Hypnograms were inspected to identify epochs of contiguous sleep stages lasting at least 5 min. These criteria yielded 39 subjects. Included are 70 epochs of W and 38 epochs of SWS. Apparent propagation of intrinsic activity was assessed by applying our previously published methodology for computing lags between rs-fMRI time series (Mitra et al. 2014). Results Fig. 1A exhibits lag projection maps in W and SWS. Lag projections depict whether a voxel is early (blue) or late (red) compared to the whole-brain mean. The temporal scale is ±0.75 s. Although several features are preserved in W vs. SWS, there are also significant differences. One of the most prominent effects is in thalamus, which is early during W, but late during SWS. Fig. 1B exhibits thalamus-referenced lag maps, where each voxel is early or late compared to a mean thalamic time-course. The temporal scale is ±1 s. During W, cortex is late with respect to thalamus, whereas during SWS, cortex is early with respect to thalamus. Despite thalamo-cortical reversal, lags within the brainstem-thalamic axis

are preserved (pink circles). Conclusions Apparent propagation of slow intrinsic activity, as measured by rs-fMRI, is altered in SWS as compared to W. In particular, intrinsic activity propagates from thalamus to cortex during W, but in the reverse direction during sleep. These results are consistent with thalamic gating of sensory information during sleep, and shed light on the mechanisms of SWS.



Disclosures: **A. Mitra:** None. **A. Snyder:** None. **E. Tagliazucchi:** None. **H. Laufs:** None. **M.E. Raichle:** None.

Poster

815. Sleep: Systems

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Swartz Foundation

Howard Hughes Medical Institute

Title: Nonlinear dynamical sleep spindle detection using delay differential analysis

Authors: ***A. L. SAMPSON**[1,2], C. LAINSCSEK[1,2], S. S. CASH[3,4], E. HALGREN[2], T. J. SEJNOWSKI[1,2];

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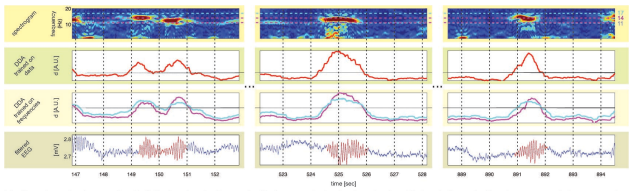
Abstract: Since nonlinear data analysis works upon the dynamical structure of the data, it allows for classification in near real time of raw data. Here, we use delay differential analysis (DDA), which is a time domain classification framework based on embedding theory. An embedding reveals the nonlinear invariant properties of an unknown dynamical system (here the brain) from a single time series (here electrocephalogram (EEG) data). The embedding in DDA serves as a low-dimensional nonlinear functional basis onto which the data are mapped. Since the basis is built on the dynamical structure of the data, preprocessing of the data is not necessary, and the low dimensionality removes the risk of overfitting. A model that was trained on a single EEG channel from one subject can be applied to a wide range of data from different subjects, channels, and recording systems. Given these desirable properties, DDA is ideally suited to the problem of sleep spindle detection. Sleep spindles are 11-17 Hz oscillations recorded in the EEG during stage 2 sleep. As sleep spindles are thought to arise from the activity of thalamocortical circuitry, they have become a subject of study for their potential roles in memory consolidation and other cognitive functions. In light of their potential importance, a method for reliably identifying spindles in real time is needed. DDA analyses were applied to intracranial recordings from patients with intractable epilepsy and compared to traditional wavelet methods. As a bridge between these two methods, an additional DDA classifier was built on simulated data (noise-diluted harmonics) to detect frequency bands. One single set of DDA parameters can be used for 15 tested recordings. The mean area under the receiver operating characteristic curve is 0.75. DDA is a powerful method for improving the sensitivity of EEG analyses to transitory time series features that does not rely on any post-hoc adjustment of outputs or tailoring to individual subjects.



The figure shows the abovementioned spindle detection algorithm results. The lowest row in the plot shows the data with the spindles marked by a human expert. In the next row, the DDA frequency band detector outputs are shown (in blue for a 11-17 Hz band and in magenta for a 11-14 Hz band). In the next row, the DDA output (trained on one channel from a different subject) is shown. We also show the spectrograms for reference.

Lainscsek, C. Sejnowski, T.J. Delay Differential Analysis of Time Series, Neural Computation, 27, 594-614, 2015

Disclosures: **A.L. Sampson:** None. **C. Lainscsek:** None. **S.S. Cash:** None. **E. Halgren:** None. **T.J. Sejnowski:** None.

Poster

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Topic: E.08. Biological Rhythms and Sleep

Support: CIHR (MOP-130502)

Title: GABA receptors on orexin and MCH neurons are differentially regulated following sleep deprivation and recovery

Authors: *H. TOOSSI, E. DEL CID-PELLITERO, B. E. JONES;
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Abstract: Orexin (Orx) and melanin concentrating hormone (MCH) neurons play opposite roles in the regulation of sleep-wake states, Orx neurons discharging during waking (W) and MCH neurons reciprocally so during sleep, including slow wave sleep (SWS) and REM or paradoxical sleep (PS) (Hassani et al., 2009). In the present study, we examined in mice whether GABAA and GABAB receptors (Rs) are present on Orx and MCH neurons and might undergo differential changes as a function of their activity following sleep deprivation (SD) and sleep recovery (SR). Applying quantitative stereological image analysis of dual immunofluorescent stained sections, we determined that the proportion of Orx neurons bearing GABAARs was significantly higher following SD (~48%) as compared to sleep control (SC) and SR (~24% and ~27%, respectively) and that the luminance of the GABAARs was also significantly higher. In contrast, the average proportion of the MCH neurons bearing GABAARs was significantly lower following SD (~43%) in comparison to SC and SR (~54% and ~56%, respectively) and the luminance of the GABAARs was also significantly lower. Although, GABABRs were observed in all Orx and MCH neurons (100%), the luminance of these receptors was differentially altered following SD. The intensity of GABABRs in the Orx neurons was significantly higher after SD than after SC and SR, whereas that in the MCH neurons was significantly lower. The present results indicate that GABARs undergo dynamic and differential changes in the wake-active, Orx neurons and sleep-active, MCH neurons as a function of and homeostatic adjustment to their preceding activity and sleep-wake state.

Disclosures: H. Toossi: None. **E. del Cid-Pellitero:** None. **B. E. Jones:** None.

Poster

815. Sleep: Systems

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NIH Grant 5 T32 EY 20503-5

ONR MURI award N000141310672

Howard Hughes Medical Institute

Title: The large-scale spatiotemporal structure of spindle oscillations in human sleep

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Abstract: During stage II sleep, neocortical circuits exhibit transient epochs of narrowband oscillations in the 11-15 Hz frequency band. The physiological substrate for these "spindle" oscillations is the interplay of activity within the thalamus, providing transient synchronization across the neocortex through thalamocortical feedback loops. Although there is increasing evidence that spindles are involved in the consolidation of long-term memories, the specific neural mechanisms by which this occurs remain unclear. Evidence from electroencephalography suggests large-scale coherence across the cortex during spindles, but their specific spatiotemporal structure during natural sleep is not well understood. In this work, we study electrocorticogram (ECoG) recordings of patients during stage II sleep and apply phase-based methods to characterize the spatiotemporal dynamics. During spindling activity, the ECoG array exhibits a specific, robust spatiotemporal pattern: large-scale rotating waves traveling from parietal to temporal to frontal to parietal cortex. These recurring spatiotemporal patterns are observed in the left and right hemisphere of individual patients and extend over tens of milliseconds, placing the neural assemblies they synchronize on a timescale relevant to spike-time dependent synaptic plasticity. Finally, we introduce a method to detect phase-based motifs in narrowband signals, in order to study precise fluctuations of activity within these recurring spatiotemporal patterns. We find indeed that precise phase relationships during spindles on the electrode array recur across several minutes of sleep, further demonstrating the precision and importance of relative timing among electrodes during sleep oscillations in humans. --
Acknowledgments: The authors would like to thank the clinical subjects for their participation in the research. All research was approved by the local institutional review board, and electrode

placement was determined solely by clinical criteria. This work was supported by NIH (R01 NS-036449 and 5 T32 EY 20503-5), ONR (MURI award N000141310672), and Howard Hughes Medical Institute.

Disclosures: **L.E. Muller:** None. **G. Piantoni:** None. **S.S. Cash:** None. **E. Halgren:** None. **T.J. Sejnowski:** None.

Poster

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Topic: E.08. Biological Rhythms and Sleep

Support: MURI: N000141310672

Title: Reduced computationally efficient model for slow wave sleep activity

Authors: N. F. RULKOV[1], G. P. KRISHNAN[2], S. CHAUVETTE[3], I. TIMOFEEV[4], *M. V. BAZHENOV[5];
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Abstract: During stage 3/4 of NREM sleep, brain activity is dominated by slow (0.2 - 1 Hz) oscillations consisting of periodic transitions between active (or Up) and silent (or Down) states in the membrane voltage of excitatory and inhibitory neurons. Experimental and modeling studies suggest that Up-states are initiated due to progressive accumulation of spontaneous miniature EPSPs, maintained by recurrent excitatory connections and terminated by progressive activation of the intrinsic inhibitory currents, synaptic depression and synaptic inhibition. Previous models based on Hodgkin-Huxley type models showed that the combination of the intrinsic and synaptic mechanisms is sufficient for recreating basic properties of slow oscillations. We previously developed a class of reduced and computationally efficient map-based neuronal models for large-scale neuronal simulations. In this study this approach was extended to capture intrinsic neuronal properties necessary to generate sleep slow oscillations. Map-models use difference equations capturing dynamics of a neuron in discrete moments of time with relatively large intervals (~0.5msec). It provides a significant reduction in computational resources that are required for computer simulation of neurons and large-scale

networks. We show that addition of nonlinear dynamical bias and activity dependent depolarization to the previously developed map-based model can mimic the effects of K+ leak and persistent Na+ currents , which are required for modeling sleep slow oscillation. A network of map-based pyramidal cells and inhibitory interneurons with synaptic connectivity similar to the cortical structure demonstrated the onset of slow oscillations that closely match the activity observed in experiments and in the conductance-based models. The high computational efficiency of this new approach makes it feasible for large-scale analysis of spatio-temporal dynamics and synaptic plasticity in multi-dimensional cortical models.

Disclosures: **N.F. Rulkov:** None. **G.P. Krishnan:** None. **S. Chauvette:** None. **I. Timofeev:** None. **M.V. Bazhenov:** None.

Poster

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Topic: E.08. Biological Rhythms and Sleep

Support: MURI: N000141310672

NIH: R01 MH0996

NIH: R01 EB009282

Title: Structural connectivity between cortex and thalamus determines temporal features of sleep spindles

Authors: *G. P. KRISHNAN[1], M. J. CHOINSKI[1], L. E. MULLER[2], D. J. HAGLER, Jr[3], S. S. CASH[5], T. J. SEJNOWSKI[2], E. HALGREN[4], M. BAZHENOV[6];
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Abstract: Sleep spindles are waxing and waning oscillatory activity (at 11-15 Hz) observed during stage II sleep. Individual spindles last about 0.3-2 seconds and recur at intervals from 2 to 15 seconds. MEG and EEG show significant differences in spindle occurrences, with about 50% of MEG spindles occurring without EEG spindles whereas only 15% of EEG spindles occur alone [1]. Spindles generated in the thalamus recruit cortical circuits. A core subsystem projects

focally to layer 4 of the cortex and a matrix subsystem projects more diffusely to apical dendrites of layer 5 neurons in layer 1. We previously hypothesized that difference between MEG and EEG signals may reflect difference between those projections [2]. In this study, we used computational modeling and laminar recordings from epilepsy patients to identify the mechanism that results in differences in spindle occurrence across different cortical layers. Laminar recordings showed higher probability of spindle occurrence (based on automated spindle detection) in middle layers (putative layers 3/4) compared to deeper layers (putative layers 5/6). Using a reduced thalamocortical model with only one cortical layer (with pyramidal and inhibitory neurons) and a corresponding thalamic network (thalamocortical and reticular neurons) we found that the interspindle interval and the probability of spindle occurrence in a given interval decreased with increases in the level of spontaneous miniature excitatory synaptic activity and increases in the fanout (number of efferent neurons connected) of thalamocortical and corticothalamic connectivity. We then simulated a multilayer cortex model, which included three layers for cortex (layer 3/4, 5 and 6) and separate thalamic neurons for core and matrix subsystems. The fanout of the thalmocortical and corticothalamic projections between matrix thalamic neurons to layer 5 neurons was made to be wider than the core thalamic neuron projections to layer 3/4. In the full model, spindles occurred more often in layer 3/4 than in layer 5, with a shorter median inter-spindle interval. In addition, the spindles in layer 5 were more synchronous across neurons compared to layer 3/4. Overall, this study demonstrates that differences in the projections between thalamus and cortex may determine the spatiotemporal features of spindle activity across cortical layers. References 1. Dehghani N, Cash SS, Halgren E (2011) Emergence of synchronous EEG spindles from asynchronous MEG spindles. Hum Brain Mapp 2. Bonjean M, Baker T, Bazhenov M, Cash S, Halgren E, et al. (2012) Interactions between Core and Matrix Thalamocortical Projections in Human Sleep Spindle Synchronization. J of Neuroscience

Disclosures: **G.P. Krishnan:** None. **M.J. Choinski:** None. **L.E. Muller:** None. **D.J. Hagler:** None. **S.S. Cash:** None. **T.J. Sejnowski:** None. **E. Halgren:** None. **M. Bazhenov:** None.

Poster

815. Sleep: Systems

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Topic: E.08. Biological Rhythms and Sleep

Support: NS051305

NS076980-01

Title: Enhanced sleep does not change light responsiveness

Authors: S. DISSEL[1], L. KIRSZENBLAT[2], J. DONLEA[3], M. KLOSE[1], R. WINSKY-SOMMERER[4], B. VAN SWINDEREN[2], *P. SHAW[5];
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Abstract: We recently reported that we could enhance sleep and thereby restore memory in the classic mutants rutabaga and dunce as assessed using both Aversive Phototaxic Suppression (APS) and courtship conditioning. In the APS, flies are individually placed in a T-maze and allowed to choose between a lighted and darkened chamber over 16 trials. During 16 trials, flies learn to avoid the lighted chamber that is paired with an aversive stimulus (quinine/ humidity). During review, an anonymous reviewer was adamant that our dataset was confounded: “Light responsiveness is influenced by sleep state, therefore, using a memory assay that is dependent on light response is a significant confound”. This claim was surprising since 1) sleep impacts all sensory modalities, 2) we test memory in awake behaving flies and 3) we included a large dataset demonstrating that sleep did not alter either photosensitivity or quinine sensitivity during waking. When queried further, the reviewer changed their minds noting that: ““it has long been known that light impacts sleep (Shang et al., 2008 and Shang et al., 2011)”. This was also surprising since this conclusion is contrary to the observation that sleep was increased primarily during the biological day when lights are on. Despite the large amount of contradictory evidence, both in our manuscript and the literature, we conducted a series of new experiments to further evaluate the reviewers’ hypotheses. We report that neither moderate nor extreme levels of sleep-induction impact photosensitivity over a range of light intensities ranging from ~100 lux to ~7,000 lux. Moreover, increased sleep did not alter fast phototaxis or the amount of locomoter activity following a light pulse. Importantly, sleep did not differentially alter the phase response curve following a 10 minute light pulse administered at either ZT-15 or ZT-21 compared to controls. Finally, we report that increased sleep does not change the response properties of PIGMENT DISPERSING FACTOR-neurons to dopamine as measured by Epac signaling as implied by the reviewers’ references. Consistent with our original results, we conclude that the increased sleep does not alter light responsiveness in flies.

Disclosures: S. Dissel: None. **L. Kirszenblat:** None. **J. Donlea:** None. **M. Klose:** None. **R. Winsky-Sommerer:** None. **B. van Swinderen:** None. **P. Shaw:** None.

Poster

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Support: Fyssen Foundation

ONR N00014-13-1-0672

NIH R01 EB009282

NIH R01 MH099645

ECOR-MGH Research Scholars Award

Title: Possible human sleep replay of cortical activity patterns evoked by motor sequential learning

Authors: *J.-B. EICHENLAUB[1], X. WU[2], E. HALGREN[3], S. S. CASH[1];
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Abstract: It is now widely believed that the sleeping brain plays a key role in memory consolidation, and numerous studies have highlighted the occurrence of replay as a neural mechanism underlying such sleep-dependent consolidation. This concept, that neural activity during sleep recapitulates waking activity in a precise fashion, was first described in rodents with the identification of 'place cells'. These cells respond selectively to locations in space, and consequently fire in a sequential order while animals are trained to run along a given path. Importantly, these cells fire again in that same sequence during subsequent sleep, 'replaying' the initial run experience. In humans, neuroimaging studies have reported that brain structures involved in learning were reactivated during subsequent sleep, suggesting the occurrence of replay in human sleep as well. However, direct, electrophysiological evidence of replay in human is still lacking. Here, subjects implanted with macro-electrode arrays for long-term epilepsy monitoring were taught to produce a motor sequence before a nap. The task required the participants to press four numeric keys on a standard computer keyboard, repeating one sequence (e.g. 4-2-1-3-4-1) "as quickly and accurately as possible" for a period of 30 seconds. For each subject, the nap period following learning was scored off-line, and its hypnogram computed. Another sleep period, preceding the learning, was selected and used as baseline. NREM sleep (N2 and N3) were predominant during sleep periods. The analysis of the behavioral data revealed that the time to correctly execute the sequence decreased across 30s-trials, showing a gradual acquisition of the motor sequence during learning. To investigate the occurrence of

motor replay during sleep, we applied the template matching method developed by Louie and Wilson (2001). This method allows quantification of the degree of similarity between the spatiotemporal activity pattern during learning ("template") and those recorded during sleep periods ("targets"). Spatiotemporal patterns in the beta- (15-25Hz) and gamma- (70-110Hz) bands were analyzed separately. Our preliminary results show that the targets from a period of sleep after motor learning exhibit higher levels of similarity with the template than targets from a period of sleep preceding the learning, especially in the gamma band. These results suggest that the spatiotemporal dynamics of gamma activity that support motor learning are reproduced during subsequent sleep, providing direct, neurophysiological evidence for replay in human sleep.

Disclosures: J. Eichenlaub: None. **X. Wu:** None. **E. Halgren:** None. **S.S. Cash:** None.

Poster

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Topic: E.08. Biological Rhythms and Sleep

Support: NIH Grant RO1HL116845

Title: Behavior of noradrenergic A7 neurons during sleep and wakefulness

Authors: *V. B. FENIK[1,2], S. J. FUNG[1,2], M. H. CHASE[1,2], I. RUKHADZE[1];
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Abstract: The activity of hypoglossal motoneurons (HMs) is essential for maintaining upper airway patency. Therefore, a sleep-related depression of HM activity plays an important role in the pathogenesis of Obstructive Sleep Apnea. A loss of excitatory noradrenergic (NA) drive to HMs that is provided by pontine A7 neurons has been suggested to largely contribute to the depression of HMs during rapid eye movement (REM) sleep (Fenik et al., 2008). We sought to determine whether the behavior of A7 neurons during sleep and wakefulness supports their suggested role in sleep-related depression of HMs. Sprague-Dawley rats were chronically implanted for chronic recording of the EEG and neck EMG under surgical anesthesia. Experiments were conducted in head-restrained animals after they were fully adapted and displayed normal sleep-wake patterns. Spontaneous discharges of single units were isolated extracellularly in the A7 region (depth 6.6-8.5 mm from the cerebellum surface) on both sides using standard glass electrodes filled with sodium acetate that contained Pontamine Sky Blue to

iontophoretically mark recording sites. Brain sections were immunostained for tyrosine hydroxylase to visualize NA neurons and verify recording sites. Of the 30 units that were recorded in the A7 region, six were classified as A7 neurons based on the location of their recording sites, patterns of activity and durations of their action potentials. The A7 neurons were silent during REM sleep whereas other units that also had a state-dependent pattern of activity increased their firing rate during REM sleep (n=6), non-REM sleep (n=1) or during REM sleep and wakefulness (n=2). During non-REM sleep and wakefulness, A7 neurons had tonic low-frequency discharges. Their average firing rates were not different between non-REM sleep (0.97±0.4 (SE) spike/s) and wakefulness (1.06±0.2 spike/s, n=6, p=0.8, t-test). The average duration of their action potentials (including after-potentials) were larger than that of other units that were recorded with a bandwidth of 0-3000 Hz (2.2±0.2 ms (range: 1.8-3.1 ms, n=6) vs. 1.3±0.1 ms (range: 0.8-2.0 ms, n=10); $p<0.01$). Our findings suggest that A7 neurons are silent during natural REM-sleep. This is in agreement with their suggested role in the depression of HMs during REM sleep. Unexpectedly, we also found that the firing rates of A7 neurons are similar during both non-REM sleep and wakefulness. This finding does not support the role of A7 neurons in the inhibition of HMs during non-REM sleep and suggests that HMs are inhibited during non-REM sleep via different mechanisms.

Disclosures: **V.B. Fenik:** None. **S.J. Fung:** None. **M.H. Chase:** None. **I. Rukhadze:** None.

Poster

815. Sleep: Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 815.22/Z24

Topic: E.08. Biological Rhythms and Sleep

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CIHR Doctoral Fellowship

Harvard Society of Fellows

Title: Intracranial and EEG-based measures of sensory-evoked network dynamics in human cortex during emergence from general anesthesia

Authors: ***E. A. MUKAMEL**[1], L. D. LEWIS[2], G. PIANTONI[3], E. N. ESKANDAR[4], R. A. PETERFREUND[6], E. N. BROWN[5,7], S. S. CASH[3], P. L. PURDON[6];

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Abstract: During emergence from general anesthesia, the brain transitions out of the unconscious state and recovers its ability to process complex sensory information and coordinate behavior. Previous studies have suggested that this process is not simply the reverse of an anesthetic induction, but rather involves a distinct sequence of brain states. We studied emergence from general anesthesia in human subjects using both intracranial and scalp-based (EEG) measures of cortical activity. In the first study, we performed intracranial electrocorticography (ECoG) from 12 patients with pharmacologically intractable epilepsy, who had intracranial electrodes placed for clinical reasons. Patients were studied as they emerged from propofol general anesthesia, and the times of their first movement and first voluntary response to a verbal command were recorded. Auditory stimuli were presented every 3.5-4.5 seconds to assess the neural response to sensory information. We observed that after the propofol infusion was stopped, low-frequency power in cortex gradually decreased but patients remained unresponsive to stimuli for several minutes. During this period, a subset of auditory stimuli evoked large-amplitude field potentials lasting ~0.5-1.5 seconds. During these evoked responses, high-frequency (>30 Hz) power was suppressed, suggesting that auditory stimuli induced cortical DOWN-states. Both the morphology and spatial distribution of evoked waves were similar to K-complexes observed during non-rapid eye movement (NREM) sleep in the same patients. We next validated and extended these findings in healthy subjects using non-invasive EEG. We analyzed data from a previously reported study of 10 subjects in which 64-channel EEG was recorded during induction and recovery from propofol general anesthesia. Auditory stimuli were presented to subjects at 2 s intervals, and these stimuli included names, words and clicks. As in the intracranial recordings, we observed large-amplitude, slow (~1 s duration) sensory-evoked potentials during the recovery from general anesthesia, but before subjects regained the ability to respond to the stimuli. These results suggest that a brain state occurs during emergence from general anesthesia that shares some properties with stage 2 NREM sleep. In this state, slow oscillations are reduced compared with the anesthetized state and cortex is desynchronized and active, while sensory stimuli evoke cortical DOWN states. We propose that this phenomenon could be due to different recovery rates in cortical and thalamic structures, leading to a state in which cortex has recovered from anesthesia but thalamic nuclei remain suppressed.

Disclosures: **E.A. Mukamel:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. **L.D. Lewis:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. **G. Piantoni:** None. **E.N. Eskandar:** None. **R.A. Peterfreund:** None. **E.N. Brown:** E. Ownership Interest (stock, stock

options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Masimo Corporation. F. Consulting Fees (e.g., advisory boards); Masimo Corporation. **S.S. Cash:** None. **P.L. Purdon:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Masimo Corporation. F. Consulting Fees (e.g., advisory boards); Masimo Corporation.

Poster

815. Sleep: Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 815.23/Z25

Topic: E.08. Biological Rhythms and Sleep

Support: MURI grant N000141310672

Title: Understanding the mechanisms of hippocampal reactivation: from CA3 to CA1

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Abstract: Declarative memory consolidation involves interaction between cortex and hippocampus during sleep. Memory replay - repeatable sequences of pyramidal cell firing - has been demonstrated during sleep, and has been associated with characteristic brain oscillations, giving rise to the hypothesis that these may form the critical neural substrate of memory consolidation. The content of hippocampal replay can be biased during sleep, in what is called cued-reactivation, and such paradigms show enhanced memory performance in humans. Moreover, tampering with replay can disrupt memory formation and consolidation. Despite extensive evidence highlighting the importance of replay within the broader phenomenon of sleep-mediated memory consolidation, the neural mechanisms underlying hippocampal sequence replay are still unknown. During sleep, replay events are associated with specific patterns of neuronal oscillations. Replay is seen in cortex during slow oscillation - a rhythmic (< 1Hz) state in which periods of activity (active or Up states) alternate with quiet periods (silent or Down states), while replay in area CA1 of the hippocampus is associated with sharp-wave ripple events - brief irregular bouts of high frequency (>150 Hz) firing, driven by strong excitatory inputs coming from CA3, seen as a strong deflection in the LFP in the stratum radiatum (the sharp wave). We build on our previous research to develop a model of hippocampal spike sequence replay during sleep. In the past, we have introduced a model of CA1 ripples in which oscillations

are transients, mediated by the intrinsic frequency of CA1 basket cells driven by CA3 activation. In this work, we construct a model of CA3 in which stochastic intrinsic activation of pyramidal cells triggers a massive cell activation that results in a strong excitatory input to area CA1. We observe that sequential activation of a selected sub-group of CA1 pyramidal cells is driven by a less specific sequential activation in CA3. We use the model to study differences in CA3 and CA1 during sharp-wave ripples, and compare it to *in vivo* recordings in CA3 and CA1. We also characterize the mechanisms underlying sequence selection and reactivation within a sharp-wave ripple event. At the end, we use this hippocampal model to investigate the role of cortical inputs on ripple timing and their specific spike content. Our study illustrates the possible role of cortical Up states during slow oscillations in biasing hippocampal replay, which is a core component of the cortico-hippocampal interaction underlying memory consolidation.

Disclosures: P. Malerba: None. **S. Nagl:** None. **G.P. Krishnan:** None. **J. Fellous:** None. **M. Bazhenov:** None.

Poster

815. Sleep: Systems

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Topic: E.08. Biological Rhythms and Sleep

Support: ONR (MURI: N000141310672)

NIH (R01 MH0996)

NIH (R01 EB009282)

Title: Interactions between cortical slow oscillations and hippocampal sharp-wave ripples during slow wave sleep

Authors: *P. SANDA, P. MALERBA, G. P. KRISHNAN, M. BAZHENOV;
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Abstract: During stage 3/4 of NREM sleep the entire cortical network periodically alternates between silent (Hyperpolarizing, or Down) and active (Depolarizing, or Up) states with a period around 0.5-1 sec. In the CA1 region of hippocampus, activity bursts known as ripples emerge and are accompanied by sharp waves originated by activity in CA3 region and forming so called sharp wave ripples complexes (SWR). It has been proposed that information acquired during the day is quickly stored in the hippocampus and consolidated into long-term memory via

progressive sleep-mediated cortico-hippocampal interaction, in particular during slow-wave sleep. The exact mechanism of sleep-dependent consolidation is not yet understood, but experimental data suggest that hippocampal replay occurs during SWR. SWRs activity in CA1 is feed forward into cortex and interacts with its slow oscillatory dynamics, while cortical activity poses major input to the hippocampal complex, thus leading to a cortico-hippocampal loop. The precise form of the interactions within this loop is not known. In this study we present a computational model consisting of a thalamocortical network, which faithfully reproduces Up and Down states occurring during stage 3/4 NREM sleep in cortex and a hippocampal model including areas CA3 and CA1, which generates SWR activity. The SWR influenced the initiation of Up state in the cortical network with the likelihood of transition from Down to Up state increasing immediately following SWR. Further, the location of Up state initiation was dependent on specific firing of CA1 pyramidal cells during SWR. The effect of the SWR on the Up state initiation was dependent on the connectivity between hippocampal and cortical networks. Our study presents a model of how interaction between thalamocortical and hippocampal networks during sleep may organize timing of the major sleep elements - slow oscillation and sharp wave ripples complexes - as required for declarative memory consolidation.

Disclosures: **P. Sanda:** None. **P. Malerba:** None. **G.P. Krishnan:** None. **M. Bazhenov:** None.

Poster

815. Sleep: Systems

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 815.25/Z27

Topic: E.08. Biological Rhythms and Sleep

Title: Graph theoretical characterisation of functional connectivity changes in transitions between wakefulness and sleep: Evidence from human MEG source space

Authors: *A. B. STEVNER[1,3], G. PIANTONI[4], G. COLCLOUGH[2], A. BAKER[2], Y. VAN DER WERF[5], J. CABRAL[1,6], G. DECO[6], E. VAN SOMEREN[5], M. WOOLRICH[2], M. L. KRINGELBACH[1,3];
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Abstract: Sleep remains a mystery to neuroscience. Much has been learned from animal studies about the fundamental characteristics of sleep stages and the switching between them, establishing circuits in the brainstem, hypothalamus and the basal forebrain as important regulators of the sleep process, however the fundamental question of why we need to sleep is still left unanswered. Meanwhile, human evidence is compiling in favour of a strong and causal link between disordered sleep and mental illness, making the understanding of sleep more than an epistemological venture, and clinically highly relevant. Thus far, the isolated focus on the basic subcortical sleep regulators has been found insufficient in explaining the complex symptomatology of sleep disorders, and thus more recently attention has been directed towards the role of the cortical dynamics in sleep. The thriving development within the field of human neuroimaging, such as fMRI, EEG, and MEG, focussing on the large-scale patterns of spontaneous brain activity and characterising these in terms of functional connectivity, graph theory, and whole-brain computational modelling, has made it possible to test and apply more precise spatio-temporal hypotheses about the neuronal basis of sleep. One such hypothesis concerns the development of large-scale functional brain networks in the descent from wakefulness to deep sleep. Small-worldness is a global graph theoretical measure, which estimates the balance between integration and segregation of information in a network and has been successfully applied to describe structural as well as functional brain connectivity. Interestingly, large-scale networks derived from human sleep data recorded with EEG and fMRI respectively show conflicting results on this measure; with EEG sensor space networks becoming increasingly small-world from wakefulness to deep sleep across a range of frequency bands (Ferri et al 2008), and fMRI networks moving towards randomness in light sleep compared to wakefulness and deep sleep (Spoormaker et al 2010). Taking advantage of MEG's high temporal resolution, compared to fMRI, and robust source reconstruction methods, compared to EEG, we have revisited this question by applying state-of-the-art analysis methods of functional connectivity on MEG sleep data from 11 healthy participants. Estimating the small-worldness of source space networks in four different frequency carrier bands taken from periods of wakefulness, light sleep and deep sleep, we provide evidence in favour of the results from the fMRI study with a move towards randomness in light sleep being particularly clear in the theta and beta band.

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Poster

815. Sleep: Systems

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Topic: E.08. Biological Rhythms and Sleep

Support: ONR Grant N00014-13-1-0672

Title: Evidence for human memory replay in cortex: an electrocorticographical study of spatiotemporal patterns in high gamma

Authors: *X. JIANG[1], I. SHAMIE[1], S. S. CASH[3], T. THESEN[4], E. HALGREN[2]; [1]Neurosciences, [2]Neurosciences/Radiology, UCSD, La Jolla, CA; [3]Neurol. Service, Massachusetts Gen. Hosp., Boston, MA; [4]Neurology/Radiology, New York Univ. Sch. of Med., New York, NY

Abstract: In slow-wave sleep, replay of hippocampal and neocortical activity that occurred in waking has been proposed as a mechanism of memory consolidation. Most previous studies have focused on the reactivation of spatio-temporal patterns comprising focal groups of neurons in the rodent hippocampus. However, given the broad activation of human neocortex in wakeful experiences and the high information volume in episodic memories, memory replay likely involves much larger neuron ensembles. In the human cortex, activities in the High Gamma band correlate with changes in local firing, and are associated with memory encoding. Recurrence of similar spatio-temporal High Gamma activity patterns in waking and in slow-wave sleep, therefore, may be indicative of memory replay. We analyzed long-term human electrocorticographical recordings to reveal consistent spatio-temporal pattern templates of highly distributed High Gamma activity in waking; these templates were used to match the High Gamma activity in the slow-wave sleep periods preceding ("Pre-sleeps") and following ("Post-sleeps") the waking period. In all subjects, the number of templates with more Post-sleep matches were significantly larger than that of templates with more Pre-sleep matches, providing evidence that human memory replay may occur in the cortex at a large scale.

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Poster

815. Sleep: Systems

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Topic: E.08. Biological Rhythms and Sleep

Support: Swiss Natl Sci Found 146244

Title: Distinct neural and cardiac parameters define the intermediate sleep state in mouse

Authors: *L. M. FERNANDEZ, A. LUTHI;
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Abstract: Human non-rapid eye movement sleep (NREMS) is subdivided into three major stages, each with distinct spectral characteristics and functional roles in sleep. In contrast, rodent NREMS is widely considered comparatively homogeneous. This notion is increasingly starting to change, as mouse NREMS not only shows on-going microarchitectural fluctuations (see Abstract by Lecci et al), but also exhibits a transitional period prior to REMS onset, also called Intermediate Sleep (IS). During IS, the cortex continues to show typical NREMS EEG features, such as sleep spindles (8-15 Hz), while oscillations characteristic for REMS, i.e. theta activity (6-10 Hz), already appear. To define whether IS represents a distinct sleep state, we asked: 1) Does IS display polysomnographic characteristics (EEG combined with EMG and ECG) distinct from consolidated NREMS? 2) Can we identify IS-specific neural circuit constellations generating distinct local field potential activity? 3) Can we attribute IS-specific neuronal discharge patterns in rhythm-generating neurons? 4) Does IS show cardiac activity patterns distinct from those of NREMS (high vagal tone) and REMS (high sympathetic tone)? To answer these questions, we explored sleep in habituated head-restrained mice, assessing behavioral states through conventional polysomnography (EEG/EMG), and we recorded simultaneously local field potentials (LFP) from high-impedance (~10-12 MOhm) electrodes chronically implanted in the dorsal hippocampus (dCA1) and in somatosensory (S1 and S2), auditory (A1), piriform (Pir), and medial prefrontal (mPFC) cortices. To establish IS structure (onset-offset) and spectral characteristics, common oscillatory events of NREMS and REMS were examined during IS: delta (1-4Hz), theta, spindles, ripples (150-250Hz), together with muscle tone progression toward REMS atonia, and the heart rate variability as an indicator of sympathovagal balance. The functional organization between areas and neural circuits was explored during IS and compared to NREMS and REMS. Furthermore, as spindles are prominent oscillatory events during IS, we recorded unit activity at their site of origin in the reticular thalamic nucleus. Our study broadens the view of rodent NREMS as a non-homogeneous state and identifies IS as a distinct constellation of neural and cardiac activities that point to a unique cortico-thalamic-hippocampal crosstalk associated with a switch in cardiac output.

Disclosures: L.M. Fernandez: None. **A. Luthi:** None.

Poster

815. Sleep: Systems

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Topic: E.08. Biological Rhythms and Sleep

Support: NIH Grant NS082876

NIH Grant NS077408

Title: Elevating endogenous trace amine-associated receptor 1 tone promotes wakefulness

Authors: *M. D. SCHWARTZ[1], S. W. BLACK[1], J. B. PALMERSTON[1], S. B. SMITH[1], A. HARMEIER[2], M. C. HOENER[2], S. R. MORAIRTY[1], T. S. KILDUFF[1];
[1]Ctr. for Neurosci., SRI Intl., Menlo Park, CA; [2]Neurosciences Res., F. Hoffmann-La Roche, Ltd., Basel, Switzerland

Abstract: Trace amines (TAs) are endogenous amino acid metabolites that are structurally similar to the biogenic amines. TAs are endogenous ligands for trace amine-associated receptor 1 (TAAR1), a GPCR that modulates dopaminergic, serotonergic, and glutamatergic activity. Selective TAAR1 full and partial agonists exhibit similar pro-cognitive, antidepressant- and antipsychotic-like properties in rodents and non-human primates, suggesting TAAR1 as a novel target for the treatment of neurological and psychiatric disorders. Additionally, TAAR1 partial agonists are wake-promoting in rats, suggesting that TAAR1 is a previously-unrecognized component of an endogenous wake-modulating system. We previously reported that TAAR1 knockout mice (KO) exhibit increased sleep at lights-on and increased EEG gamma power (30-100 Hz) compared to WT littermates, and that the selective TAAR1 partial agonist RO5263397 increased waking and suppressed REM sleep in WT but not KO mice. Here, we report that TAAR1 overexpressing (OE) mice, in which TAAR1 is ectopically expressed throughout the brain, exhibit a complementary sleep/wake phenotype to TAAR1 KO mice and that the TAAR1 full agonist RO5256390 disrupts sleep in WT mice. TAAR1 KO, OE and WT mice were instrumented for EEG and EMG recording and implanted with telemetry transmitters for monitoring locomotor activity (LMA) and core body temperature. Following recovery, mice were recorded continuously under 12:12 LD conditions. OE mice spent more time awake over a 24h period compared to WT littermates and exhibited sustained waking during a 6h sleep deprivation compared to WT littermates. EEG spectral power was decreased in the theta (4-9Hz) and gamma bands compared to KO mice, with WT spectra intermediate between them. RO5263397- and caffeine-induced waking was potentiated in OE mice compared to WTs. In separate studies, the full agonist RO5256390 administered p.o. at ZT6 suppressed REM sleep, increased wake bout number and reduced NREM bout duration. In summary, elevating TAAR1 tone via overexpression or pharmacology tends to increase waking and decrease high-frequency EEG activity, whereas TAAR1 deletion has the opposite effect. TAAR1 partial agonism may

have greater wake-promoting efficacy than full agonism. Studies to evaluate the effects of these compounds on sleep-wake regulatory brain populations are in progress.

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Poster

815. Sleep: Systems

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Topic: E.08. Biological Rhythms and Sleep

Support: NIH 123331

NIH 124576

Title: Incomplete behavioral and neurological recovery following chronic short sleep

Authors: *S. C. VEASEY, R. XIN, P. FENIK, G. ZHAN, Y. ZHU;
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Abstract: Chronic intermittent short sleep is pervasive in modern society, where it is generally believed that weekend catch up sleep restores brain function and health. We recently determined that short sleep across a 1 wk period results in metabolic injury to and loss of locus coeruleus neurons. Here we tested the hypothesis that metabolic injury, neuron loss and wake impairments do not fully recover with 4 wk recovery sleep. We found, not only a loss of locus coeruleus neurons (50% reduction, $p<0.001$), but also orexin neurons (40% reduction, $p<0.001$), yet the adjacent sleep-active melanin-concentrating hormone neurons conferred protection. Neuron stereologic counts remained reduced after 4 wk recovery, while wake impairments and metabolic stress persisted. Persistence of lipofuscin in wake-active locus coeruleus and orexinergic neurons along with reduced sirtuin type 1, support the concept that chronic intermittent sleep loss prematurely ages select populations of neurons, including locus coeruleus and orexinergic neurons. In light of the irreversible locus coeruleus injury and loss, the work provides a potential link between chronic short sleep and neurodegenerative processes.

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Poster

816. Motor Learning

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 816.01/Z32

Topic: F.01. Human Cognition and Behavior

Title: Global connectivity changes in procedural learning and cognitive training

Authors: ***A. NIKOLAIDIS**, T. TALUKDAR, A. BARBEY, A. KRAMER;
Univ. of Illinois Champaign Urbana, Urbana, IL

Abstract: Cognitive training aims to use paradigms that make demands on cognitive and motor systems such that participants improve on untrained tasks, a phenomenon known as transfer. These transfer effects show promise for future cognitive training research, yet they are often difficult to replicate. These failures to replicate are due to a lack of understanding how training induces changes in the brain, and subsequently how these changes drive transfer. Prior research suggests that over the course of training, the procedural, motor, and cognitive networks involved in task acquisition and performance should change as training progresses; however, experimental evidence and understanding of how training remodels these networks is lacking. In the current study, participants trained for 20 to 30 hours with a multimodal computerized training paradigm called Space Fortress that places demands on motor control, short-term memory, and executive control. At pre and post training, participants were scanned using fMRI while playing Space Fortress in the MRI scanner. We examine how global brain connectivity changes from pre to post training using multivariate distance-based matrix regression (MDMR). This analysis technique can be used to investigate whether inter-individual whole-brain connectivity patterns are related to variation in one or more phenotypic variables of interest (e.g. clinical diagnosis, behavioral performance, intervention groups). Using MDMR, we investigate which brain regions demonstrate significant changes in global connectivity profiles from pre to post training. We find a set of motor areas, such as the left precentral and postcentral gyrus, visual-attention areas, such as the lateral occipital cortex, and regions implicated in executive function, such as the anterior cingulate cortex and paracingulate cortex, which change significantly in global connectivity from pre to post training (FDR corrected $p < 0.05$). Using descriptive post hoc analyses, we extract graph theoretic properties of the networks involved in these regions, and assess what network topological properties change as a function of training. These results characterize network

reorganization that occurs as a function of a complex multimodal cognitive training paradigm, and motivate future work into descriptions of network plasticity during training.

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Poster

816. Motor Learning

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Program#/Poster#: 816.02/Z33

Topic: F.01. Human Cognition and Behavior

Title: Focus of attention has differential effects upon short-latency afferent inhibition across practice

Authors: L. Y. SUZUKI, *S. K. MEEHAN;
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Abstract: Instructions orienting the attention of the learner towards elements of the environment (an "external focus") rather than the action of their body (an "internal focus") have been shown to enhance learning. While the benefits of an external focus have been quantified extensively using behavioral measures the neural substrates of the external focus are less understood. The purpose of the current study was to investigate changes in motor cortical networks throughout motor practice under different foci of attention. Two groups of participants practiced a discrete sequence of finger movements under differing instructions that emphasized and internal or external focus of attention. The external focus (EXT) group was instructed to concentrate on pressing the correct keys. The internal focus (INT) group was instructed to concentrate on moving the correct fingers during the sequence. To determine changes in intracortical networks, the magnitude of short-latency afferent inhibition (SAI) was quantified in first dorsal interosseous muscle (FDI) using motor evoked potentials elicited by single pulse TMS at various points during practice. For both groups retention of both behavior and changes in SAI was assessed 24 hours post-practice. We hypothesized that SAI of FDI MEPs would be reduced across practice for both groups, however, the extent of SAI reduction would be greatest for the EXT group. Further, we hypothesized that SAI of FDI MEPs evoked during key presses in the sequence not involving the FDI would be reduced for the EXT but not INT group during late practice blocks and the retention test. Preliminary results support our hypotheses, SAI was reduced to a greater extent in the EXT compared to INT group on elements in the sequence that required index finger movement following practice. Further, for elements of the sequence not involving the FDI, the reduction in SAI in the FDI was greater for the EXT group compared to

the INT group. These results suggest that an external focus of attention promotes greater plasticity and formation of muscle synergies.

Disclosures: **L.Y. Suzuki:** None. **S.K. Meehan:** None.

Poster

816. Motor Learning

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Topic: F.01. Human Cognition and Behavior

Support: RO1HD053793

T32HD007414-20

Title: Cognitive processes contribute to behavioral gains during motor reconsolidation

Authors: ***N. F. WYMBS**[1,3], A. J. BASTIAN[2,3], P. A. CELNIK[1,2];
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Abstract: Reconsolidation mediates the updating of consolidated memory. We have recently shown that a motor skill is strengthened when the reactivated skill is practiced in an environment that promotes increased sensorimotor variability. This gain appeared to be mediated by top-down strategic processing. Since strategy is supported through cognitive control processes, we wondered if taxing these processes could affect the expression of skill strengthening. To test for the role of cognition during motor skill reconsolidation, we used a dual-task procedure during the reconsolidation intervention. In 3 sessions (4 blocks of 30 trials each), participants learned to control the lateral displacement of a cursor to a sequence of 5 targets using a logarithmic transduction of pinch force (SVIPT). Following the initial session (0 hr), participants returned after a 6-hour delay (period needed to consolidate the task) and the following day (24 hr). During session 2 (6 hr), participants reactivated the skill and then either continued to train on the original SVIPT, or instead, on a modified version of the original SVIPT that we have previously shown to strengthen skill through reconsolidation. During this session participants also performed a secondary auditory frequency discrimination task. This required deciding if the last tone in a series was higher or lower in frequency than the first tone. We manipulated cognitive load: one group received high load, hearing as many as 4 tones in series, whereas a second group received low load and always heard 2 tones. We quantified the effect of the intervention, or skill

strengthening, as the pre/post intervention change in original SVIPT skill (first block 24 hr - last block 0 hr). We found that skill strengthening was blocked when performing the modified SVIPT under high cognitive load, but preserved when participants were exposed to the modified SVIPT under low cognitive load. Similar to our previous results, we found that repeated training on the original SVIPT during the intervention had little effect on skill strengthening. Further, the high load condition blocked within-session (session 2) performance improvement regardless of exposure to the modified or original SVIPT intervention. However, low load did not affect within-session improvement during the modified SVIPT. Interestingly, we found that participants that benefitted the least from the modified SVIPT intervention also had the lowest accuracy on the tone task when tested under high load. These findings suggest that strengthening of a motor skill following reconsolidation involves top-down strategic processing after the reactivation of a consolidated skill.

Disclosures: **N.F. Wymbs:** None. **A.J. Bastian:** None. **P.A. Celnik:** None.

Poster

816. Motor Learning

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 816.04/Z35

Topic: F.01. Human Cognition and Behavior

Title: The effects of action observation on obstacle avoidance strategies in patients with chronic stroke

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Abstract: Functional locomotor disability is a common consequence of stroke and much attention has been recently given to the use of alternative training strategies to promote motor rehabilitation for individuals with stoke. This study was designed to investigate how task-oriented training using action observation influence rehabilitation of locomotor behaviors during obstacle crossing in stroke patients. Eighteen patients with chronic stroke participated in the experiment and were divided into two groups: an action observation group (n=9) and a non-action observation group (n=9). Patients in the experimental group practiced obstacle crossing tasks after watching video clips showing a normal obstacle crossing action while patients in the control group underwent the same procedure of rehabilitation training except for the video clips.

Patients participated in a 6-week training program, 3 times per week for 1 hour per session. The primary finding indicated that there were greater increases in knee flexion in the experimental group particularly for increased obstacle heights after the training. In contrast, no significant change was found for other measures of gait parameters between groups following intervention. Taken together, these findings suggest that the use of action observation intervention strategy potentially optimizes functional locomotor performance such as obstacle crossings in stroke by incorporating motor imagery, especially when observing movements with intent to imitate.

Disclosures: Y. Song: None. **J. Park:** None.

Poster

816. Motor Learning

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 816.05/Z36

Topic: F.01. Human Cognition and Behavior

Support: Ludvig og Sara Elsass Fond

Title: Visuomotor skill learning and accompanying changes in corticospinal excitability: Causal relation or epiphenomena?

Authors: *L. CHRISTIANSEN[1,2], E. BOJSEN-MØLLER[1,2], M. A. J. MADSEN[1,2], R. THOMAS[1,2], J. B. NIELSEN[1,2], J. LUNDBYE-JENSEN[1,2];
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Abstract: *Objectives* Skill acquisition is accompanied by increased corticospinal excitability and motor cortical representations. It is unclear whether these changes relate to the process of skill acquisition or task performance as shown in expert musicians and athletes. To address this question we compared the effects of a progressive (PT) versus non-progressive (NPT) long-term motor learning protocol. We hypothesized that progressively increasing task difficulty during training would cause incremental increases in corticospinal excitability and improved motor performance. *Methods* Two groups of subjects practiced a visuomotor task requiring precise abduction-adduction control of the fifth digit. Task difficulty remained constant in the NPT group whereas it was progressively increased in the PT group. Corticospinal excitability was assessed through application of transcranial magnetic stimulation of the primary motor cortex prior to and following 2, 4 and 6 weeks of training and after 8 days of detraining. *Results* After 6 weeks, both groups improved visuomotor performance at the baseline task difficulty with no

between-group difference. In contrast, the PT group demonstrated significantly better visuomotor performance at an advanced task level. Both groups showed increased corticospinal excitability after 2, 4 and 6 weeks of training in terms of a decline in motor threshold, but only the PT group demonstrated larger maximal motor evoked potentials with long-term training. *Conclusions* The study demonstrates that progressively increasing task difficulty during visuomotor skill acquisition is accompanied by improved motor skill performance and additional changes in corticospinal excitability. The findings underline the importance of continuously challenging patients and athletes in order to maximize recovery and performance. Corresponding Author: Lasse Christiansen Department of Exercise and Sport Sciences & Department of Neuroscience and Pharmacology Panum Institute, University of Copenhagen, Blegdamsvej 3, 2200 Copenhagen N, Denmark. Email: lassech@sund.ku.dk

Disclosures: L. Christiansen: None. **E. Bojsen-Møller:** None. **M.A.J. Madsen:** None. **R. Thomas:** None. **J.B. Nielsen:** None. **J. Lundbye-Jensen:** None.

Poster

816. Motor Learning

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Program#/Poster#: 816.06/Z37

Topic: F.01. Human Cognition and Behavior

Title: Increases in cognitive effort diminishes the contextual interference effect

Authors: C. A. AIKEN, A. T. MOSS, *A. W. VAN GEMMERT;
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Abstract: Research has shown that practicing a task in the context of other tasks leads to improved retention performance of the task(s). This phenomenon is commonly referred to as the contextual interference effect (Shea & Morgan, 1979; Lee & Magill, 1985). A potential explanation for this phenomenon is that the amount of cognitive effort increases as the amount of contextual interference increases which results in improved learning (Lee, Swinnen, & Serrien, 1994). The purpose of this study was to investigate the effects of increased cognitive effort on the contextual interference effect. 47 individuals volunteered to participate in the study. All participants learned three variations of a graphic aiming task that required them to draw from one target (r=0.5cm) to another target (r=0.5cm) while avoiding a stationary barrier within exactly two, three, or four seconds. Each task was repeated 30 times; however, the schedule structure of training was either blocked (i.e., 30 trails of each task in sequence) or random (i.e., the three tasks randomly distributed across the 90 trials). Half of the participants performed these tasks

only, while the other half of the participants performed the timed aiming tasks with a secondary arithmetic task to increase cognitive effort (i.e., the 47 participants were distributed over the 4 groups). Five minutes following acquisition, a 6 trial random retention test was performed. The dependent variables were calculated using the criterion and movement time; i.e., absolute error (AE), constant error (CE), and variable error (VE). Acquisition was analyzed with separate 2 (schedule) x 2 (cognitive effort) x 2 (block: first and last block of acquisition) mixed factors ANOVAs for AE, CE, and VE. 2 (schedule) x 2 (cognitive effort) x 2 (block: first acquisition block and retention) mixed factor ANOVAs were applied to measure retention. During acquisition all groups significantly decreased AE ($p<.001$). Increased effort resulted in more bias, i.e., higher CE ($p<.01$). There was also a main effect of schedule ($p<.05$) and effort ($p<.05$) for VE. Increased effort with more interference resulted in less consistency during acquisition. During retention there was a main effect of effort for AE ($p<.05$) with increased effort having more error. There was also a main effect of schedule for VE ($p<.05$) with blocked practice having more error during retention. Random practice increased consistency but did not increase movement time accuracy, while the increase in cognitive effort diminished the contextual interference effect for the magnitude of error.

Disclosures: **C.A. Aiken:** None. **A.T. Moss:** None. **A.W. Van Gemmert:** None.

Poster

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Program#/Poster#: 816.07/Z38

Topic: F.01. Human Cognition and Behavior

Support: MEXT KAKENHI 15K17329

Title: Contributions of finger movements to cognitive tasks

Authors: *Y. ITAGUCHI, C. YAMADA, K. FUKUZAWA;
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Abstract: The present study investigated the relationships between motor action and cognitive processing with particular reference to kanji-culture individuals. Kanji-culture individuals often move their finger as if they are writing when they are solving cognitive tasks, for example, when they try to recall the spelling of English words. This behavior is called kusho, meaning air-writing in Japanese. However, its functional role is still unknown. To reveal the role of kusho behavior in cognitive processing, we conducted a series of experiments, employing two different

cognitive tasks, a construction task and a stroke count task. Methods In total, 159 students participated in the experiments, and were assigned to one of four experiments: 1) kusho elicit tasks, 2) a character construction task, 3) other versions of the character construction task, and 3) a stroke count task. Except for the experiment 1, the participants executed the tasks in three hand conditions; participants were instructed to use either kusho, unrelated finger movements or do nothing during the response time. To isolate possible visual effects, two visual conditions in which participants saw their hand and the other in which they did not, were introduced. In the experiment 1, we examined the frequency of the occurrence of spontaneous kusho behavior, and in the other experiments we recorded the number of correct responses and response time as measures of the task performance. Results and Discussion The results showed that kusho behavior has different functional roles in the two types of cognitive tasks. In the construction task, the visual feedback from finger movement facilitated identifying a character, whereas the kinetic feedback or motor commands for the behavior did not help to solve the task. In the stroke count task, by contrast, the kinetic aspects of the finger movements influenced counting performance depending on the type of the finger movement. Regardless of the visual condition, kusho behavior improved task performance and unrelated finger movements degraded it. These results indicated that motor behavior contributes to cognitive processes.

Disclosures: Y. Itaguchi: None. **C. Yamada:** None. **K. Fukuzawa:** None.

Poster

816. Motor Learning

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Topic: F.01. Human Cognition and Behavior

Support: NINDS Clinical Neuroscience Program

Title: Primary motor cortex inhibition depresses non-motor procedural learning

Authors: *E. M. WASSERMANN[1], P. J. KOSHY[1], A. STEEL[2], D. BAGEAC[1], L. WILKINSON[1];
[1]NIH/NINDS, Bethesda, MD; [2]NIH/NIMH, Bethesda, MD

Abstract: Previous research has shown that inhibitory repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex (M1) impairs motor sequence learning, but not basic motor function, e.g., reaction time and movement speed. It is not known, however, if the effect is specific for motor forms of procedural learning or whether M1 stimulation affects

procedural learning in general. To investigate this question, we tested the effect of M1 inhibition on the weather prediction task (WPT), a probabilistic categorization task with no motor learning component, under two behavioral conditions. In a between groups design in healthy individuals, we delivered rTMS, using the continuous theta-burst (cTBS) paradigm, for 40 s with a real or sham coil, after which subjects performed the WPT. In the WPT, subjects are required to learn an arbitrary, probabilistic, association between a set of meaningless cue cards and arbitrary outcomes, i.e. if the weather will be rainy vs. fine or hot vs. cold. Subjects indicated their responses by pointing and clicking with a mouse. In the "Feedback" condition, subjects were told whether their response was correct and received monetary reward/punishment after each trial of 150 trials. In the "Observational" condition, subjects observed cue-outcome associations passively and were then tested on their knowledge with 150 trials without feedback. The conditions were performed in separate sessions. The proportion of correct responses was calculated for blocks of 50 trials. Compared to sham, cTBS over M1 reduced performance significantly in the last (3rd) block in the Feedback condition, while observational learning was unaffected. Inhibitory rTMS of M1 seems to impair procedural learning even when the motor demand of the task is minimal. Explicit (observational) learning appears to be spared. We infer that M1 is part of a network with a general role in procedural learning.

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Poster

816. Motor Learning

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Title: Altered human memory modification in the presence of normal consolidation

Authors: *N. CENSOR[1,2], E. R. BUCH[2], K. NADER[3], L. G. COHEN[2];
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Abstract: Following initial consolidation during which the memory is stabilized, subsequent modification of memory strength and its reconsolidation are crucial for further learning. Yet, it is not clear whether consolidation and memory modification are the same or different processes. Here, we report disrupted memory modification in the presence of normal consolidation of human motor memories, which relate to different structural features of white-matter integrity. Chronic stroke patients and healthy aged-matched controls performed a sequence of finger movements on three separate days. On Day 1 performance was tested immediately after training. On Day 2 subjects performed test trials to measure consolidation from Day 1 and to reactivate the originally trained memory. On Day 3, they performed retest trials to evaluate memory modification from Day 2. Patients showed efficient initial consolidation (mean performance gains between Days 1 and 2 of 25.6%±8.6% standard error, $P<0.03$). However, memory modification was impaired (no significant performance gains between Days 2 and 3, -8.9%±7.7%, $P=0.45$). Consolidation and memory modification magnitudes were significantly different ($P<0.03$). Impairments were evident only when the memory was reactivated and could not be explained by a ceiling effect on performance. Age-matched healthy controls showed efficient consolidation but showed also efficient memory modification (10.6%±2.6%, $P<0.004$), significantly higher than patients ($P<0.02$). Memory modification impairments were then related to structural network architecture using a graph-theoretical network analysis approach and to local white matter microstructural integrity using diffusion-weighted MRI. We measured the degree to which each nodal brain region integrates information between all other nodal pairs in the structural network, nodal betweenness centrality. Memory modification only correlated with the difference in nodal betweenness centrality between patients' and normals' networks in the contralesional medial-frontal gyrus (MFG, $r=0.83$; $P<0.005$). We then related memory modification with extralesional white-matter microstructural integrity, measured as fractional anisotropy (FA). Memory modification only correlated with FA in three contralesional hemisphere white-matter regions ($P<0.005$): underlying MFG, the vicinity of the precentral gyrus and the anterior intraparietal area. The results reveal mechanistic differences between consolidation and subsequent memory modification in human procedural learning. This knowledge may help guide interventional strategies to enhance brain function and resulting behavior.

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Poster

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Human Frontiers Science Project Organization (HFSPO) (CDA00078/2011-C) and Israel Science Foundation (grants No. 1771/13 and 2043/13)

Title: M1 activity during action observation co-varies with subsequent behavioral changes in spontaneous rate of execution

Authors: *N. ARIDAN[1], R. MUKAMEL[1,2];
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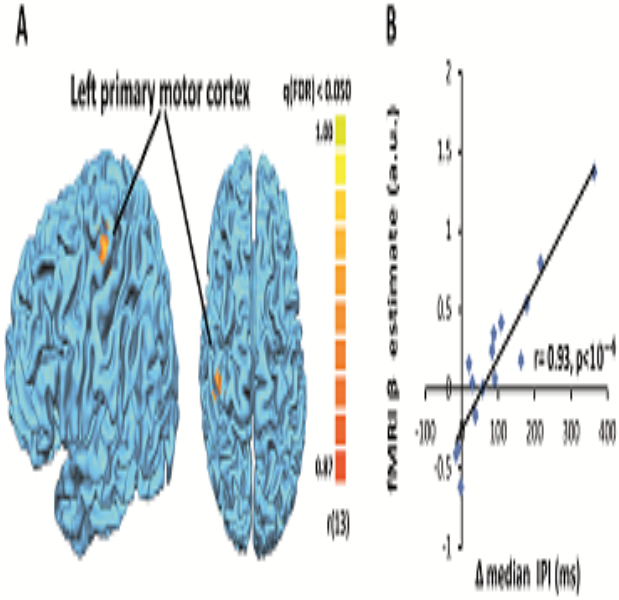
Abstract: Observation of people performing movements facilitates motor planning, execution and motor memory formation. Rate, an important feature in the execution of repeated movements, has been shown to vary following movement observation although the underlying neural mechanisms are unclear. The discovery of regions in the monkey and human brain which share representations of execution and observation of motor actions may provide the neural infrastructure for such adaptations. In this study, we examined whether: first, the rate of self-paced index finger-pressing is implicitly modified following passive observation of a similar action performed at a different rate; second, in which brain regions the fMRI BOLD signal during action observation co-varies with the change in the subsequent spontaneous rate of execution. In the first experiment, fifty subjects performed a finger pressing sequence with their right hand at their own pace before and after passive observation of a video depicting the task performed at 3 Hz by someone else. Across subjects, spontaneous execution rate had a bimodal distribution with modes of 2 and 4.2 Hz. Following video observation, the slower subjects performed the task at an increased rate. In the second experiment, an additional set of 15 subjects performed the task in the fMRI scanner and observed a 4 Hz video. We found positive correlation between fMRI signal in the left primary motor strip during video-observation and implicit behavioral change in task performance rate ($r=0.89$, corrected for $q(FDR)< 0.05$). We conclude that observing someone else perform an action at a higher rate, implicitly increases the endogenous rate of execution and that this implicit induction is mediated by activity in the contralateral primary motor-cortex.



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Poster

816. Motor Learning

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Topic: F.01. Human Cognition and Behavior

Support: KTIA NAP 13-2-2015-0002

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Title: Dynamical changes of functional connectivity during implicit memory formation

Authors: ***B. TOTH**[1], Á. TAKÁCS[2], Z. ZAVECZ[2], A. KÓBOR[3], K. JANACSEK[4,5], D. NEMETH[4,5];
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Abstract: Sequence learning is a prominent component of skill learning, which is involved in obtaining not only motor but also cognitive and social skills. However, the neural basis of the formation of this fundamental learning mechanism still remains poorly understood. The present study aimed to investigate 1) the functional connectivity (FC) networks which promote successful implicit sequence memory formation 2) and the dynamical changes of network connectivity as a function of time during learning. Young adults (N = 28) performed the Alternating Serial Reaction Time (ASRT) task while 128 channel EEG recording was performed. ASRT can measure general skill and sequence-specific learning. Phase synchronization in 7 frequency bands was used to quantify FC between cortical regions during the first, second, and third part of the learning task. According to the results of linear regression analysis, the sequence-specific learning performance was associated with an increase of FC in the posterior brain regions exclusively mediated by fast brain oscillations (beta) together with a decrease of FC in the frontal network driven by slow oscillations (theta, delta). In line, a prominent decline of FC in slow oscillatory networks together with an increase of FC in fast oscillatory network was observed as a function of time elapse. Our results indicate that implicit learning processes are provided by fast oscillation in posterior cortices while frontal slow rhythms linked with attentional monitoring. In conclusion, a dynamic antagonist relationship between the brain networks of automatic and controlled processes may serve a hallmark of implicit sequence learning.

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Poster

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Title: Learning an internal representation of a deep convolutional neural network model for pose-based human action recognition

Authors: *J.-C. PARK, Y. JANG, C. NAM, J. JUN, H. CHOI, D.-S. KIM;
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Abstract: How humans recognize and imitate others motor actions? It has been an important issue in the cognitive developmental robotics research to explain the internal mechanism of humans' action learning process and to make an intelligent robot mimicking an ability of humans. Hence, there have been computational studies using a neural network model to recognize and imitate human motor behaviors. A Deep Neural Networks (DNN) which consist of multi-layered Convolutional neural networks (CNNs) in these days has successfully extracted most relevant features hierarchically for recognizing visual objects. Moreover, they are learned positional-invariant feature by itself from dataset due to a subset of connection weight is shared. They also have been used to extract spatiotemporal features of time-series for an audio classification. In this study, we designed a deep neural network model which consists of a CNN, fully connected feedforward neural network and softmax neural network to be able to classify a sequence of human actions. The HDM05 dataset, which is a motion capture dataset containing more than 70 motion classes, was used to train our model. An input of the network, therefore, is a set of normalized vectors containing joint angles which length is T. The lengths of each input data T represents the lengths of the motor sequence. Due to duplication issue, we used 65 motion class reduced by merging redundant classes. To improve the robustness of the local movement (e.g. moving only left arm), the first layer is splitted into the five CNNs of which input are five sub-part of the whole body (head, left arms, right arms, body, left leg, and right leg). The network was trained with the backpropagation algorithm with a loss function which are reducing a classification error. As a result, the fully-trained network showed 75% of classification accuracy. Additionally, we visualized internal representation of the first convolutional layer, and relevant spatiotemporal motion features were found. It means that an agent equipped with a deep neural network can successfully recognize 65 different motor behaviors. Furthermore, it may memorize its experience as a set of primitive actions. To reveal this more precisely, we plan to investigate the internal representation of the higher layers by using up-to-date visualization technique for the deep convolutional neural networks for the future works.

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Poster

816. Motor Learning

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 816.13/Z44

Topic: F.01. Human Cognition and Behavior

Title: Effects of cerebellar transcranial direct current stimulation on fine motor sequencing skill

Authors: ***R. E. SHIMIZU**[1], A. D. WU[2], X. GUO[1], B. J. KNOWLTON[1];
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Abstract: The cerebellum plays a significant role in motor learning (c.f., Doyon et al., 2003) and performance (e.g., Horwitz et al., 2000). Anodal transcranial direct current stimulation (tDCS) applied to the cerebellum has been demonstrated to increase excitability (Galea et al., 2009). The current study examined the effect of cerebellar anodal tDCS on learning and performance on a fine motor sequencing task. During a training phase, participants practiced three 8-element key press sequences in a non-repeating, interleaved order while receiving either anodal ($N = 23$) or sham ($N = 21$) stimulation. A transfer phase immediately followed in which participants received three novel sequences in an interleaved order. No stimulation was given during the transfer phase. A main effect of stimulation condition was found such that the anodal group had faster response times compared to the sham group during the training phase ($p = .019$) and during the transfer phase ($p = .032$). Furthermore, the anodal group exhibited learning over time during the training phase ($p = .005$) but the sham group did not ($p = .449$). Thus, anodal tDCS to the cerebellum resulted in online enhancement of performance, and this effect continued to last after the cessation of stimulation. This post-stimulation benefit occurred for sequences that had not been practiced in the training phase when stimulation was delivered. These results suggest that tDCS may be a relatively inexpensive yet effective way to improve fine motor skills.

Disclosures: **R.E. Shimizu:** None. **A.D. Wu:** None. **X. Guo:** None. **B.J. Knowlton:** None.

Poster

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Support: NIH Grant R01DC011755

Title: Procedural memory is not uniformly intact in individuals with traumatic brain injury

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Abstract: Memory deficits are common following traumatic brain injury (TBI). A long held assumption is that declarative memory is disproportionately impaired while procedural memory is left intact. In fact, preserved procedural memory is often suggested as a possible mechanism to leverage in rehabilitation and efforts aimed at new learning (e.g., errorless learning; positive everyday routines). This assumption, however, has not received extensive empirical study, nor has there been a systematic examination of the different forms of procedural memory. Given that TBI is associated with diffuse neural damage, we hypothesized that the underlying neural structures supporting different forms and aspects of procedural memory would be vulnerable in TBI and some percentage of patients would have procedural memory deficits. The current study examines the acquisition and maintenance of different forms of procedural memory in a group of individuals with TBI (N=18) and a group of healthy comparison participants with no history of neurological disease or injury, demographically matched to each patient. Participants with TBI varied in severity from mild to severe, were at least 6-months post-injury and were recruited from the Iowa Traumatic Brain Injury Registry. All participants were tested on a comprehensive battery of procedural memory tests including Rotor Pursuit (RP), a measure of motor learning, Mirror Tracing (MT), a perceptual skill, and the Serial Reaction Time Task (SRT), which measures sequence learning, a cognitive skill. We repeated the battery on a subsequent visit 3 to 6 months later. On the initial visit, we found that 17 of the 18 (94%) participants with TBI were impaired on at least one of the procedural memory tasks (44% impaired on RP; 50% impaired on MT; 56% impaired on SRT) and that 8 of the 18 (44%) were impaired on 2 or more of the tasks. Those individuals with TBI who demonstrated learning on a given task on the initial visit were able to maintain this learning on the subsequent visit, indicating that leveraging procedural memory in rehabilitation efforts may benefit certain patients. These results suggest that the procedural memory system is not uniformly intact following TBI and challenges the traditional view that procedural memory is largely preserved in TBI. These results also suggest individualized interventions based on specific patterns of memory impairment (within and across memory systems) may be a more fruitful approach towards the rehabilitation of TBI.

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Poster

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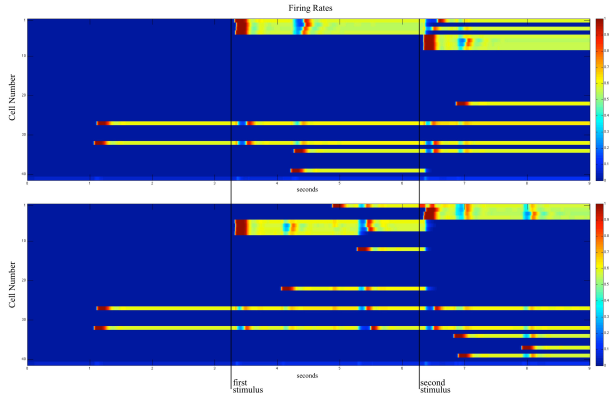
Topic: F.01. Human Cognition and Behavior

Support: The Swartz Foundation

Title: Spatiotemporal discrimination and recall in neural networks with short-term synaptic plasticity

Authors: *P. MILLER[1], B. SHLAER[2];
[2]Swartz Ctr. for Theoretical Neurosci., [1]Brandeis Univ., Waltham, MA

Abstract: Strongly coupled pools of cells in recurrently connected neural networks exhibit bistability, which allows for stimulus information to persist for very long times. However, it is difficult for such pools to encode temporal information about a sequence of stimuli without short-term synaptic plasticity. Synaptic depression is a biophysically described transient decrease in synaptic transmission strengths caused by increased presynaptic activity which destabilizes attractor states and thus causes the network to move along trajectories that depend on the temporal content of stimulus sequences. It has been shown that such a network can independently encode stimulus amplitude, duration, and numerosity (Miller, P., Front. Comput. Neurosci. 7:59, 2013), which makes it a strong candidate for successful encoding of spatiotemporal information. We demonstrate the capability of such a network to discriminate different spatiotemporal stimuli. We also show that such networks can perform both discrimination and recall tasks. Additionally, we demonstrate that the experimentally known phenomena of primacy (fewer task errors involving the first few stimuli) and recency (fewer task errors involving the last few stimuli) are reproduced in those networks able to accumulate information across long sequences of stimuli. Shown in the figure below is the neural activity within a network receiving two successive stimuli. Despite starting from the same state, the activity resulting from AB (top) is distinct from that resulting from BA (bottom). Additionally, stimulus A alone (top middle) or B alone (bottom middle) are distinct from all states, including the initial state (left of either).



Disclosures: **P. Miller:** None. **B. Shlaer:** None.

Poster

816. Motor Learning

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 816.16/AA3

Topic: F.01. Human Cognition and Behavior

Support: RO1AG036863

F31AG047037

Title: Caudate functional connectivity mediates the association between mindfulness and implicit learning

Authors: ***C. M. STILLMAN**[1,4], X. YOU[5], K. L. SEAMAN[7], E. C. RASMUSSEN[2], C. J. VAIDYA[2,6], R. S. TURNER[3], J. H. HOWARD, Jr.[8,3,9], D. V. HOWARD[2,9];
[1]Dept. of Psychology, [2]Psychology, [3]Neurol., Georgetown Univ., Washington, DC; [4]Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA; [5]Neurosci., [6]Children's Natl. Med. Ctr., Washington, DC; [7]Psychology, Yale Univ., New Haven, CT; [8]Psychology, The Catholic Univ. of America, Washington, DE; [9]Ctr. for Brain Plasticity and Recovery, Washington, DC

Abstract: Accumulating evidence shows a positive relationship between mindfulness and explicit cognitive functioning, or that which occurs with conscious intent and awareness. However, two recent studies report a negative relationship between mindfulness and implicit types of learning, or those that occur without conscious awareness or intent (Stillman et al., 2014; Whitmarsh et al., 2013). This apparent dissociation between implicit and explicit processes raises the possibility that mindfulness may not be beneficial in all cognitive domains. The

negative relationship between dispositional mindfulness and implicit sequence learning (IL) reported in Stillman et al. 2014, and the potential neural mechanisms behind it, were the focus of the present fMRI study. Specifically, we examined whether the relationship is mediated by communication, or functional connectivity, of learning-relevant brain regions: the caudate and medial temporal lobe (MTL). Forty-two older adults (ages 60-90) completed the Mindful Attention Awareness Scale, followed by three event-related runs (15-min each) of an IL task, the Triplets Learning Task (TLT). In the TLT, participants respond to sequences of events in which a probabilistic regularity is embedded. Unbeknownst to them, some events occur with high (HP) and others with low probability (LP). IL is assessed by comparing reaction times to HP vs. LP events. Mindfulness was negatively associated with IL in the TLT, replicating the results of our earlier study. We next examined the neural basis of this relationship using an anatomically-defined bilateral caudate seed. Seed-based voxel-wise analyses were conducted in SPM 8 to generate connectivity maps of the seed for each subject on each run of the TLT. These maps were entered into a repeated-measures ANCOVA with session as the repeated factor and learning as the covariate of interest, and with age and overall task speed as nuisance covariates. Learning was positively associated with caudate connectivity to the MTL at all runs, as revealed by a main effect of learning in the left (peak MNI: x, y, z = -24, -13, -17; p 64, corrected) and right (x,y,z = 45, -13, -26; $p < .0005$, $k > 64$, corrected) MTL. In addition, the cross-run average connectivity between the caudate seed and both MTL clusters was negatively associated with mindfulness. Further, caudate/MTL connectivity significantly mediated the mindfulness-IL relationship. Thus, the degree of connectivity between the caudate and MTL, regions central to traditionally dissociable learning systems, may be a neural mechanism by which mindfulness impairs IL.

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Poster

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Support: I-CORE Grant 51/11

Israel Sience Foundation 1771/13 and 2043/13

HFSP CDA00078/2011-C

Title: Neural substrates of enhanced intermanual skill transfer during online manipulation of visual feedback

Authors: *O. OSSMY[1], R. MUKAMEL[2];
[1]Tel Aviv Univ., Tel Aviv, Israel; [2]Tel-Aviv Univ., Tel-Aviv, Israel

Abstract: In the realm of motor skill learning it has long been known that physical practice with one effector results also in performance gains of another (un-practiced) effector. Here, we examined the role of sensory feedback (visual and tactile), and its neural correlate, on the transfer of motor skills across hands in humans. To this end, we manipulated visual feedback of right-hand finger movement through the use of 3D Virtual Reality devices. 18 subjects learned a novel motor skill (sequence of finger movements) through physical training with their right hand, while real-time movement-based visual feedback of their left hand fingers was provided. We found that this manipulation facilitates inter-manual transfer and enhances performance gains with the untrained (left) hand. Additionally, we examined whether adding passive left-hand movement to the manipulated visual input can further enhance the transfer effect. Using a custom-built device, 18 additional subjects trained on a similar task by physical training with their right hand while their left-hand was passively moved in a yoked manner to these voluntary right-hand movements. We found that adding this passive training led to further increases in left hand performance gains. Finally, we collected functional magnetic resonance imaging (fMRI) data from an additional set of 18 subjects during physical training with the right hand, coupled with visual feedback of left-hand movement. We found that activity in the right Superior Parietal Lobule (rSPL) during training correlated with subsequent gains in left-hand performance. Optimizing the transfer of motor skills across limbs has key consequences on real-world learning (such as sports and music) and for the development of new approaches for rehabilitation of patients with unilateral motor deficits such as ALS or stroke. Our results point to the right SPL as an important node in this process.

Disclosures: O. Ossmy: None. **R. Mukamel:** None.

Poster

816. Motor Learning

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 816.18/AA5

Topic: F.01. Human Cognition and Behavior

Title: Disambiguation in the serial reaction time task

Authors: *J. L. HOELTER, C. M. KAIVER, S. J. HELD, C. E. ECHEVESTE, A. J. GREENE; Univ. of Wisconsin-Milwaukee, Milwaukee, WI

Abstract: Sequence learning is a ubiquitous aspect of learning in general, from way-finding, to procedural learning, to episodic narratives. The serial reaction time task (SRTT; Nissen & Bullemer;1987) is a widely used method to study sequence learning. In a typical task, participants respond to a sequence of repeated or random light positions with a corresponding button-press. Facilitation is observed when response latency decreases for items in repeated sequences. Generally, performance is thought to be implicit, and indeed Amnesic patients' perform at normal levels for both novel and repeated sequences. SRTT readily provides a means to address the disambiguation of related or similar sequences, (i.e. discrimination or pattern separation). As SRTT is presently used to examine implicit prediction or expectation (the previous items predict the upcoming item, which is the basis for facilitation; i.e., generalization or pattern completion), SRTT with novel and repeated sequences that include ambiguous sub-sequences, allows examination of implicit performance on task demands usually believed to require awareness. Moreover, sequence disambiguation has been demonstrated in other tasks (e.g., maze learning, which includes place learning, object identification, etc.) but as yet, not the SRTT, which is arguably the purest form of sequence learning. The present SRTT uses acoustic location, rather than visual, to examine repetition-facilitation and disambiguation. A 1 kHz tone is presented through a pair of sound-cancelling headphones, monaurally left or right, or binaurally center; participants responded with a position-corresponding button-press. The manipulation was a series of random presentations, used as a control, versus two series that included repeated sequences, each of which had an overlapping, ambiguous, middle sub-sequence. Participants were able to learn the repeated sequences, as performance button-presses were faster within repeated sequences than to random series. (c.f., REF). The critical finding is that in this auditory SRTT, participants successfully disambiguate without awareness being necessary.

Disclosures: J.L. Hoelter: None. **C.M. Kaiver:** None. **S.J. Held:** None. **C.E. Echeveste:** None. **A.J. Greene:** None.

Poster

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Support: the Israeli Center of Research Excellence (I-CORE) in Cognition (I-CORE Program 51/11)

Israel Science Foundation (grants No. 1771/13 and 2043/13)

Human Frontiers Science Project (HFSP) Career Development Award (CDA00078/2011-C)

Title: Activity in superior parietal lobule during training by observation predicts subsequent performance gains

Authors: O. OSSMY, *R. MUKAMEL;
Tel-Aviv Univ., Tel-Aviv, Israel

Abstract: A dominant idea in motor cognition links motor control with action observation. Previous behavioral and imaging studies in humans have shown that training by passive observation of actions can result in motor skill learning and performance gains. Nevertheless, the role of observed hand identity (left/right) during such training is unclear. Through the use of 3D Virtual Reality devices we generated visual input simulating the subject's real hands. 18 subjects trained on a novel motor skill (sequence of finger movements) while passively observing their virtual right or left hand performing the action. Gains in each hand (difference in performance level before/after training) were obtained. We found no difference in performance gains across hands following training by observation of left or right virtual hand. However, across subjects the correlation between left and right hand performance gains depended on the identity of the observed hand. Training by observation of the left hand yielded positive correlation between performance gains of both hands, while right hand observation resulted in a negative correlation. Next, we investigated the underlying neural mechanism of this phenomenon. We recorded functional magnetic resonance imaging (fMRI) data from an additional set of 18 subjects and found that activity in bilateral Superior Parietal Lobule (SPL) during training by observation correlated with subsequent performance gains. This was true for both tested hands and observational training condition. These results imply that in the absence of overt physical practice the bilateral SPL plays an important role in the process of learning by observation irrespective of the identity of the observed hand.

Disclosures: O. Ossmy: None. **R. Mukamel:** None.

Poster

816. Motor Learning

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Topic: F.01. Human Cognition and Behavior

Support: MEXT-Supported Program for the Strategic Research Foundation at Private Universities, 2014-2018

Title: Morphological changes in cortical microstructure of the brain by short-term training

Authors: ***Y.-W. SUNG**[1], D. KANG[2], U.-S. CHOI[3], S. OGAWA[2];
[1]Kansei Fukushi Institute, Tohoku Fukushi Universit, Sendai, Japan; [2]Kansei Fukushi Institute, Tohoku Fukushi Univ., Sendai, Japan; [3]Neurosci. Res. Inst., Gachon Univ. of Med. and Sci., Incheon, Korea, Republic of

Abstract: Most of the previous studies of neuroplasticity in system level by MRI were on long-term and intensive training such as music and physical exercise over years or months though few studies were over weeks. As for shorter timescales, several minutes of electrical and magnetic stimulation is known to cause morphological changes in the cortical microstructure of the brain. Some studies using diffusion-weighted MRI have demonstrated the microstructural changes in human. Recently a study reported microstructural changes in the motor area by short-term magnetic stimulation. In this study, we examined whether the similar period of training not by electrical or magnetic stimulation but by typical functional tasks such as finger tapping would cause the same kind of microstructural changes in the cortex. We used a paradigm in which subjects practiced a finger tapping task using both hands simultaneously and measured the brain by diffusion-weighted MRI. A series MRI scan consisted of gradient-echo echo-planar-imaging (GE-EPI) for functional MRI (fMRI), diffusion-weighted imaging (DWI) before and after the intensive finger tapping task for 15 minutes. For control, an additional scan for DWI was inserted before the training. In DWI measurements low and high b values, 300 s/mm^2 and 1200 s/mm^2, were interleaved in a measurement scan. For some subjects spin-echo images with two contrasts were acquired to examine a possibility of some other aspects of microstructural changes. DWI data were evaluated on activation maps by fMRI. Several motor areas showed statistically significant differences in DWI signals before and after the training but with no difference between two measurements before the training. Some areas of them showed the difference only for high b value and others for both low and high b values. These results suggest some microstructural changes by the training in the areas, especially the areas shown signal differences only for the high b value. This is parallel with the previous study used magnetic stimulation and shows the possibility of microstructural changes by a short period of tasks. In addition, the results give a caution about the evaluation of the data. The signal sources of the areas shown differences for both b values are considered to be large blood vessels rather than tissues.

Disclosures: **Y. Sung:** None. **D. Kang:** None. **U. Choi:** None. **S. Ogawa:** None.

Poster

816. Motor Learning

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Program#/Poster#: 816.21/AA8

Topic: F.01. Human Cognition and Behavior

Title: Impact of feedback valence during skill learning on dynamic and static functional connectivity

Authors: *A. D. STEEL[1,2], E. H. SILSON[1], C. J. STAGG[2], C. I. BAKER[1];
[1]NIH, Bethesda, MD; [2]Oxford Univ., Oxford, United Kingdom

Abstract: While valenced feedback (vFB), e.g. reward or punishment, aid performance and skill learning, we do not know how vFB is integrated in the brain. To examine the behavioral and neural changes associated with vFB, volunteers (HVs) were trained on a serial reaction time (SRT) task under three different feedback regimes (each n = 12): i) Reward (REW) - monetary reward if accurate and RT better then median reaction time (RT) on the last 100 trials, ii) Punishment (PUN) - began with $60 and money was taken away if they were inaccurate or slower than their median RT on the last 100 trials, and iii) Control (CON) - were told they would be given compensation based on their speed and accuracy and given pseudo vFB. In the SRT, a stimulus shown in 1 of 4 locations and HVs press the corresponding button. During certain trials the stimulus appears according to a fixed sequence. The difference between RT on random and sequence trials indexes skill memory, which was evaluated after short- (1-hr), intermediate- (24-48 hrs), and long- (30_ days) delays. Training was conducted inside the MRI scanner and to assess the impact of training, 20-minute resting state fMRI scans were taken before and after training. Behaviorally, during training, there was a benefit of vFB on RT irrespective of sequence type. Further, vFB (REW and PUN) benefitted early learning compared to CONT. All groups demonstrated retention across the testing sessions, with no difference between the vFB regimes. To evaluate functional connectivity, the time series from 148 ROIs were extracted. The ROI x ROI correlation was considered using the entire 20 minutes (static) or by evaluating the variation correlation pattern over time (dynamic). Static FC revealed an increase in FC between cortical and subcortical ROIs in REW, while cortical-cortical connectivity increased in CONT. PUN showed no change in static connectivity, but displayed an increase in connection variability across time. These results show that vFB differentially influences both static and dynamic FC.

Disclosures: **A.D. Steel:** None. **E.H. Silson:** None. **C.J. Stagg:** None. **C.I. Baker:** None.

Poster

816. Motor Learning

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Program#/Poster#: 816.22/AA9

Topic: F.01. Human Cognition and Behavior

Support: JSPS KAKENHI Grant Number 15K21602

Title: Combining speed- and accuracy-focused training prevents offline performance improvements in sequential motor skill

Authors: *S. K. SUGAWARA[1], Y. H. HAMANO[1,2], N. AOKI[1,2], H. YAMAZAKI-KINDAICHI[1,2], T. YOSHIMOTO[1,2], N. SADATO[1,2];
[1]Natl. Inst. for Physiological Sci., Okazaki, Aichi, Japan; [2]SOKENDAI (The Grad. Univ. for Advanced Studies), Hayama, Japan

Abstract: Motor skill is developed over time through both online and offline learning processes (Robertson et al., 2004). Motor performance can be measured by speed and accuracy. Both performances in the sequential motor skill markedly improve after the post-training offline period (Walker et al., 2002, 2003). Most of previous studies used the speed-focused training, because the accuracy-focused training is less effective according to our pilot data. However, it remains unknown whether the combination of speed- and accuracy-focused training benefit for online and offline learning process in the sequential motor skill or not. One hundred seven healthy right-handed volunteers participated in this study for two consecutive days. On the first day, two experimental groups were designed corresponding to the different types of training. On the combined group (n = 60), participants trained one sequential finger-tapping skill with both accuracy-focused mode, in which they were asked to repeatedly tap the sequence as accurate as possible for 15 sec, and speed-focused mode, in which they were required to tap same sequence as accurate and as fast as possible for 30 sec. On the other hand, in control group (n = 47), participants trained same sequential motor skill only with the speed-focused mode as well as previous studies (Walker et al., 2002; Sugawara et al., 2012). 24 hours after the training, participants in both groups came back to laboratory again and performed the surprised recall test. Two performance indexes were calculated according to previous study: speed and accuracy (Debas et al., 2010). Post-training performance by means of accuracy was significantly more prominent in combined group compared with control group ($p < .001$), while there was no group difference by means of speed ($p = .60$). For the offline learning process, 24 hours later, performance of speed and accuracy were significantly improved in control group ($ps < .001$). However, combined group did not show any significant offline improvement by means of speed or accuracy ($ps > .53$). According to these results, we concluded that the combination of speed-

and accuracy-focused training facilitate accurate motor execution across the online training, but paradoxically prevents the offline learning process. Present findings suggest that speed- and accuracy-focused trainings interact each other in the sequential motor skill formation.

Disclosures: **S.K. Sugawara:** None. **Y.H. Hamano:** None. **N. Aoki:** None. **H. Yamazaki-Kindaichi:** None. **T. Yoshimoto:** None. **N. Sadato:** None.

Poster

816. Motor Learning

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Program#/Poster#: 816.23/AA10

Topic: F.01. Human Cognition and Behavior

Title: Different cognitive functions determine visuomotor adaptation performance during time course of learning. A correlational approach

Authors: *A. M. SIMON, O. L. BOCK;
Inst. of Physiol. and Anat., German Sport Univ. Cologne, Cologne, Germany

Abstract: A recent learning model by Chein and Schneider (2012) proclaims three stages of learning, each associated with different cognitive abilities. In the first (formation) stage, learning is proposed to be associated with cognitive flexibility, creativity and a frequent change of strategies. In the intermediate (controlled execution) stage, learning is associated with inhibition and selective attention abilities. In the last (automatic execution) stage, it is related to automatic representation of previously established behaviours. The present studies use a correlational approach to evaluate whether the Chein and Schneider model can be applied to visuomotor adaptation. The cognitive functions supposedly related to the three learning stages were assessed by the Abbreviated Torrance Task for Adults (creativity index), Alternative Uses Task (divergent thinking), switching task (cognitive flexibility), Stroop task (higher-level inhibition), Go/No-Go task (lower-level inhibition), and choice reaction time tasks (automated psychomotor processing). Sensorimotor adaptation was assessed by a pointing task with 60° rotated visual feedback. Participant's adaptive performance (pointing error at movement onset) exhibited correlations with cognitive scores. Correlations with divergent thinking and with inhibition were high at the onset of learning and decreased later on. The correlation with automated processing was low at the onset of learning and increased thereafter. We conclude that cognitive abilities are differently associated with adaptive performance at different times of learning. The pattern of associations suggests that at least two of the three learning stages proposed by Chein and Schneider (2012) may apply to visuomotor adaptation. References Chein JM, Schneider W

(2012) The Brain's Learning and Control Architecture. Curr Dir Psychol 21(2):78-84. doi: 10.1177/0963721411434977

Disclosures: **A.M. Simon:** None. **O.L. Bock:** None.

Poster

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Program#/Poster#: 816.24/AA11

Topic: F.01. Human Cognition and Behavior

Support: RO1AG036863

F31AG047037

Title: Mindfulness and two forms of implicit learning in healthy young adults

Authors: ***E. L. RABINOVICH**[1], C. M. STILLMAN[2], J. H. HOWARD, Jr.[3], D. V. HOWARD[2];
[1]Psychology, Cognitive Aging Lab., Washington, DC; [2]Psychology, Georgetown Univ., Washington, DC; [3]Psychology, The Catholic Univ. of America, Washington, DC

Abstract: Dispositional mindfulness refers to a person's propensity to be attentive to stimuli in the present while disengaging from habitual actions and thought tendencies (Brown & Ryan, 2003). Previous behavioral and neuroimaging data have shown that dispositional mindfulness is associated with higher performance on explicit cognitive functions, or those requiring goal-directed intent and awareness (Robins et al., 2009). However, recent evidence suggests there may be a negative relationship between dispositional mindfulness and implicit learning, a type of learning that occurs without goal-directed intent or awareness (Stillman et al., 2014; Whitmarsh et al., 2013). The present study had two aims: First, we sought to replicate the negative relationship between mindfulness and visuospatial implicit sequence learning in a new sample and, second, we examined whether the negative relationship would extend to another type of implicit sequence learning: language sequence learning. We predicted that both kinds of implicit learning would be negatively related to mindfulness. Twenty-eight adults (M ± SD = 23.2 ± 1.54; 5 M) completed a widely used questionnaire assessing mindfulness and two tasks measuring implicit sequence learning in visuospatial and language domains. The Triplets Learning Task (TLT) assessed visuospatial sequence learning; participants view a horizontal row of four open circles, which fill in sequentially red, red, then green in discrete 3-event sequences called triplets.

Participants observe the first two red cues and respond via button press to the green targets. Unbeknownst to them, certain triplets occur with high probability (HP), and others with low probability (LP). Learning is measured via a difference score of accuracy and/or reaction time to HP vs. LP triplets. An adapted version of a statistical learning task (Saffran et al., 1996) was used to measure language sequence learning; participants are exposed to a five-minute stream of nonsense syllables comprising words from an artificial language. Afterwards, they rate their familiarity with words and part-words from the language on a five-point scale. Learning is assessed via difference scores of ratings to words vs. part-words. In both tasks, a greater difference score indicates more learning. We replicated the negative relationship between mindfulness and implicit learning in the visuo-spatial domain, but this relationship was not observed in the language domain. Therefore, the negative relationship between mindfulness and implicit learning may only generalize to specific types of implicit learning.

Disclosures: E.L. Rabinovich: None. **C.M. Stillman:** None. **J.H. Howard:** None. **D.V. Howard:** None.

Poster

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Program#/Poster#: 816.25/AA12

Topic: F.01. Human Cognition and Behavior

Support: JSPS KAKENHI Grant 15K21602

Title: The cortico-striatal network holds the memory of the sequential motor skill during the early training stage

Authors: *Y. H. HAMANO[1,2], S. K. SUGAWARA[1], H. YAMAZAKI-KINDAICHI[1,2], N. AOKI[1,2], T. YOSHIMOTO[1,2], N. SADATO[1,2];
[1]Natl. Inst. For Physiological Sci., Okazaki, Aichi, Japan; [2]SOKENDAI (The Grad. Univ. for Advanced Studies), Hayama, Japan

Abstract: Previous neuroimaging studies showed that the primary motor cortex (M1) and striatum increase their task related activation with the progression of sequential motor learning over 5 days, suggesting chronic learning dependent plastic change (Penhune et al, 2002). To test if this type of plastic change occurs in early learning stage in the order of 30 min training, we conducted functional MRI with sequential finger tapping learning by execution with maximum speed interleaved with execution with constant speed. Given the memory trace is reactivated by

retrieval (Nyberg et al. 2000), we assumed that the activity of the brain region that hold the memory trace of the motor skill increases as the learning progress when participants perform the skill with constant speed. A total of 55 normal volunteers participated, who underwent training of sequential finger tapping task with their non-dominant left hand. There were two modes: constant speed mode with 2 Hz controlled by external cue, and maximum speed mode in which participants were required to tap as fast and as accurate as possible. The task included 25 blocks of constant speed mode and 12 blocks of maximum speed mode, and was arranged in order of 3 blocks of maximum speed mode every 5 blocks of constant speed mode. The behavioral performance in the maximum-speed mode was progressively enhanced, confirming the successful acquisition of the sequential motor skill (Walker et al., 2002). During the constant-mode, the task-related activities in bilateral lenticular nucleus, and right primary motor area were linearly increased as learning proceeded. The activation of M1 was significantly positive at the first block of the learning, while that of the lenticular nucleus was not. This indicates that M1 is related to both execution and learning (Karni et al., 1995; Muellbacher et al. 2001) whereas the lenticular nucleus represents the memory trace of learned sequence rather than execution per se. Learning related decrease was observed in the bilateral cerebellum, dorsal premotor area, inferior and superior parietal lobule, right inferior frontal gyrus, dorsolateral prefrontal cortex, and left supra-marginal gyrus. Decreased activity in cerebellum suggests that the workload of error-correction decreases with learning progress. Likewise, the decrease in the fronto-parietal network may indicate the reduced need for monitoring the ongoing behavior (Albouy et al. 2012). We conclude that the memory trace of the sequential motor skill is distributed in the cortico-striatal network during early acquisition stage.

Disclosures: Y.H. Hamano: None. **S.K. Sugawara:** None. **H. Yamazaki-Kindaichi:** None. **N. Aoki:** None. **T. Yoshimoto:** None. **N. Sadato:** None.

Poster

816. Motor Learning

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Program#/Poster#: 816.26/AA13

Topic: F.01. Human Cognition and Behavior

Support: JSPS KAKENHI Grant Number 25233

Title: Different formation of muscle synergies associated with the desired motor output: simulation study using neural network model including muscle synergies

Authors: *S. HAGIO[1,2], M. KOUZAKI[1];
[1]Grad. Sch. of Human and Envrn. Studies, Kyoto Univ., Kyoto, Japan; [2]Res. Fellow of the Japan Society for the Promotion of Sci., Tokyo, Japan

Abstract: Introduction The concept of muscle synergies was supposed to simplify redundancy in motor control, which modularly organizes huge number of muscles (Hagio and Kouzaki, 2014; Tresch et al, 1999). Given that the central nervous system (CNS) organizes muscle synergies in the neural circuitry to adapt various external environments, it is hypothesized that the formation of muscle synergies would depend on the desired motor output. The neural network simulation comparing the adaptive process of muscle synergies to the different motor output would make it possible to clarify the hypothesis during the adaptation of muscle synergies. Therefore, the purpose of the present study was to reveal the formation mechanism of muscle synergies associated with the desired motor output using neural network model. Methods We used the previously-constructed neural network model including three intermediate layers, which corresponded to 1000 neurons in primary motor cortex (M1), several spinal interneurons regarded as muscle synergies and 26 muscles spanning the elbow and/or shoulder joint, respectively (Hagio and Kouzaki, 2014, SfN). The synaptic weights between M1 neurons and muscle synergies and between muscle synergies and muscles were updated to minimize the total squared error between desired input and output torques using an error back-propagation algorithm (Rumelhart et al., 1986). In the control simulation, the network was trained to produce appropriate elbow and/or shoulder torque in an isometric condition, which were uniformly distributed 12 target torques on the 2-dimensional joint torque plane with the same intensity. In the test simulation, the distribution of the desired torques was biased to 1st and 3rd quadrants or 2nd and 4th quadrants on the torque plane. We then compared the formation of muscle synergies and cortical system, which were constructed depending on the different desired torques. Results & Discussion The preferred directions of muscle synergies, in which the muscle synergy was most active, were biased to the more trained direction. According to the change of the preferred directions, the synaptic weights between muscle synergy and muscle layers were varied. These results would represent one of the most important factors to describe the previous results that a few muscle synergies were different across individuals, which CNS were adapted in the different environments (Hagio et al., 2015). Therefore, the CNS flexibly organizes muscle synergies and cortical system depending on the desired motor output. Our results also provide the significant suggestion that the neural system would reflect movement experience.

Disclosures: S. Hagio: None. **M. Kouzaki:** None.

Poster

816. Motor Learning

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 816.27/AA14

Topic: F.01. Human Cognition and Behavior

Support: Nordea-fonden

Title: Acute exercise and motor memory consolidation: The role of exercise intensity and timing

Authors: *R. THOMAS[1,2], L. K. JOHNSEN[1,2], S. S. GEERTSEN[1,2], L. CHRISTIANSEN[1,2], M. ROIG[3], J. LUNDBYE-JENSEN[1,2];
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Abstract: Background A single bout of high intensity cycling (~90% VO_{2peak}) immediately after motor skill training enhances motor memory consolidation. It is unclear how different parameters of exercise may influence this process and the underlying mechanisms are poorly understood. We hypothesize that the effects of exercise on consolidation are time-dependent with a decreasing positive effect of exercise post acquisition and investigate the role of exercise intensity and timing on motor memory consolidation. Furthermore, we explore the potential role of transient changes in corticospinal excitability (CSE) accompanying skill learning and exercise. **Methods** Sixty able-bodied male subjects (20-35 years) were randomly assigned to one of five groups that practiced a visuomotor accuracy task. 20 min post motor skill learning (MSL), subjects in Experiment A performed either a single bout of aerobic exercise at 45% (EX45) or 90% (EX90) of peak oxygen consumption (VO_{2peak}) or rested (CON). In Experiment B, two additional groups performed the same exercise protocol at 90% VO_{2peak} at 1hour (EX90+1h) and 2 hours (EX90+2h) post MSL. Randomization was stratified to ensure that the groups were matched for VO_{2peak} and baseline motor performance. Delayed retention tests of motor skill were tested 24 hours (R24) & 7 days (R7) post acquisition. Transcranial magnetic stimulation (TMS) was applied to the primary motor cortex to obtain measures of CSE, intracortical inhibition (SICI) and facilitation (SICF) before and after MSL, following exercise and in delayed retention tests. Motor-evoked potentials (MEPs) were recorded from the extensor carpi radialis muscle. **Results** Analysis of motor performance revealed no differences between groups during MSL, but differences in delayed retention tests. In Experiment A, EX90 showed a higher level of retention at R7 compared to CON. In Experiment B, EX90+2h demonstrated a level of retention at R24 and R7 equivalent to CON. **Discussion** In line with recent findings, the results show that exercise can promote motor memory consolidation. The results of Experiment A demonstrate that exercise intensity plays an important role for motor memory consolidation in favour of higher intensity aerobic exercise, while Experiment B indicates that timing of exercise is also important, with exercise immediately following motor skill learning being more efficient. Motor performance in retention tests were not related to measures of CSE at any time point indicating

that further studies are necessary to understand the physiological mechanisms leading to improvements in motor memory relating to exercise.

Disclosures: R. Thomas: None. **L.K. Johnsen:** None. **S.S. Geertsen:** None. **L. Christiansen:** None. **M. Roig:** None. **J. Lundbye-Jensen:** None.

Poster

816. Motor Learning

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Topic: F.01. Human Cognition and Behavior

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Title: Visuomotor learning in stable versus random task environments

Authors: *E. R. BUCH, V. P. BUCH, L. G. COHEN;
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Abstract: During skill learning, the human brain modulates neural interactions to generate appropriate actions for specific sets of intrinsic goals and task constraints. It is known that these network interactions are optimized through experience to generate a directed action with a high likelihood of achieving the goal, a process called visuomotor learning. Typically, visuomotor learning is studied through the application of a visual feedback perturbation that remains constant over time. In fact, multiple perturbations can be learned in a single session, albeit with some interference. In real-world tasks however, perturbations are rarely constant, but instead vary with time. Here, we investigated the behavioral and brain network features associated with learning multiple perturbations with unpredictable time-courses. We hypothesized that learning improvements would be driven by strategies that improved utilization of early movement sensory feedback, and that minimized the cost for subsequent corrective submovements. Furthermore, we attempted to differentiate network patterns that relate to performance gains in stable versus random task environments. Using MEG, we measured cortical activity while subjects performed a center-out joystick task. On each trial, subjects were instructed to move a screen cursor from a central home position to a peripheral target in as straight a line as possible. On some trials, the screen cursor feedback was rotated with respect to the joystick movement. In this case, the subject was required to learn to initiate a new action that corrected for the rotation. The perturbation was applied in two separate blocks of trials. In one block, the rotation was constant allowing participants to learn to compensate for the visual deviation (stable environment). In the

other block, the direction of the applied perturbation was randomized. We used a machine learning classifier approach to differentiate network states for each of the two conditions. We find two key results. First, in the random task environment a majority of participants evolved strategies that initially reduced the potential cost of subsequent submovement corrections. Second, further performance gains were achieved through a reduction in the initial submovement, suggesting that improved utilization of the sensory information was realized. Networks spanning prefrontal, frontal and posterior parietal regions showed specific patterns of activity depending upon the task perturbation context. These results suggest that separable functional brain networks are engaged during visuomotor learning in a manner that is dependent upon the stability of the environment.

Disclosures: E.R. Buch: None. **V.P. Buch:** None. **L.G. Cohen:** None.

Poster

817. Human Memory Processes: Encoding, Retrieval, and Consolidation

Location: Hall A

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Topic: F.01. Human Cognition and Behavior

Support: NIH grant MH55687

Title: Modulation of task demands suggests that semantic processing interferes with the formation of episodic associations

Authors: *N. M. LONG, M. J. KAHANA;
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Abstract: Although episodic and semantic memory share overlapping neural mechanisms, it remains unclear how our pre-existing semantic associations modulate the formation of new, episodic associations. When freely recalling recently studied words, people rely on both episodic and semantic associations, shown through temporal and semantic clustering of responses. We asked whether orienting participants toward semantic associations interferes with or facilitates the formation of episodic associations. We compared electroencephalographic (EEG) activity recorded during the encoding of subsequently recalled words that were either temporally or semantically clustered. Participants studied words with or without a concurrent semantic orienting task. We identified a neural signature of successful episodic association formation whereby high frequency EEG activity (HFA, 44 - 100 Hz) overlying left prefrontal regions increased for subsequently temporally clustered words, but only for those words studied without

a concurrent semantic orienting task. To confirm that this disruption in the formation of episodic associations was driven by increased semantic processing, we measured the neural correlates of subsequent semantic clustering. We found that HFA increased for subsequently semantically clustered words only for lists with a concurrent semantic orienting task. This dissociation suggests that increased semantic processing of studied items interferes with the neural processes that support the formation of novel episodic associations.

Disclosures: **N.M. Long:** None. **M.J. Kahana:** None.

Poster

817. Human Memory Processes: Encoding, Retrieval, and Consolidation

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National Institutes of Health Grant MH55687

Title: Neural context reinstatement during episodic memory retrieval with scalp electroencephalography

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Abstract: To account for the behavioral dynamics of episodic recall, memory models often posit a neural representation of the temporal context in which words are studied that gradually evolves as a function of the sequence of experienced and recalled items. A key prediction of these models is that retrieving a memory triggers reinstatement of the neural context representation that prevailed when the item was originally experienced. We have previously tested this prediction by examining intracranial electroencephalogram (EEG) data obtained from neurosurgical patients. Here we show that the same neural context reinstatement can be observed using high-density scalp EEG with healthy young adults. We recorded scalp EEG while participants studied lists of words for immediate or delayed free recall. To directly test the context-reinstatement hypothesis, we compared the oscillatory activity recorded as each item was recalled with the pattern of activity recorded when the items were originally studied. In two independent experiments we found that the pattern of activity just prior to an item's recall is similar to the pattern of activity that characterized the item's presentation, but also similar to the

activity associated with items presented near it in the list in a temporally graded fashion, replicating the intracranial EEG findings. These results establish that the neural features of content and context representation, and their dynamics, can be resolved in both intracranial and scalp EEG.

Disclosures: K. Healey: None. **M.J. Kahana:** None.

Poster

817. Human Memory Processes: Encoding, Retrieval, and Consolidation

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Topic: F.01. Human Cognition and Behavior

Support: James S McDonnell Foundation

Title: Investigating the neural oscillations involved in processing new "foil" semantic and phonological information

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Abstract: In order to remember a past event, it is often helpful to use strategic control processes in order to constrain what comes to mind during retrieval. Behavioural studies have supported this idea by demonstrating that incidental learning of "foil" words in a recognition test is superior if the subject is searching for items that were semantically encoded than if s/he is searching for items that were phonologically encoded. Here, we used electroencephalography (EEG) to understand the neural mechanisms underlying this behavioural effect. First, participants studied words using both semantic and phonological encoding tasks. Next, they performed a blocked old/new memory test, which allowed us to manipulate whether they were orienting retrieval towards semantic or phonological information. Finally, participants performed a surprise old/new recognition test on foil items that were incidentally learned during the previous semantic and phonological testing blocks. Behavioural results showed that recognition memory performance on the final old/new recognition test, was significantly better for semantic foils than phonological foils, despite the fact that these two item types only differed with respect to the type of information participants oriented towards in the first memory test. Preliminary results from time-

frequency analysis of EEG data during the first test phase revealed oscillatory activity patterns that differentially predicted successful memory for semantic and phonological foils on the final foil recognition test. Further analyses will characterize these effects in more detail with respect to frequency, spatial topography, and temporal duration in order to extend our understanding of the role of neural oscillations in memory encoding and retrieval.

Disclosures: D.A. Vogelsang: None. **M. Gruber:** None. **Z. Bergstrom:** None. **C. Ranganath:** None. **J. Simons:** None.

Poster

817. Human Memory Processes: Encoding, Retrieval, and Consolidation

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Topic: F.01. Human Cognition and Behavior

Support: NRF

Title: Early Oscillatory correlates of the problem-size effect - an event-related synchronization/ desynchronization (ERS/ERD) analysis

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Abstract: Aim: Little is known about the early oscillatory dynamics of neuronal networks involved in strategy selection during the processing of large- and small-size arithmetic problems. Our study was aimed at investigating this early oscillatory dynamics. Method: Electroencephalography (EEG) data were collected during mental arithmetic processing of single-digit addition problems in the Arabic format. Event-related synchronization/desynchronization (ERS/ERD) components where derived from the data and individual alpha frequencies (IAFs) for each subject determined and used in filtering data into lower and upper alpha bands. Intervals of interest (IOI) for statistical analysis were then determined from the onset/offset phases of the global field power (GFP) index of the obtained components and a high-resolution exact-statistical technique employed for the evaluation of oscillatory dynamic differences. Latencies of components were measured at maximum ERS/ERD post-question presentation. Results: Early ERS in lower alpha at pre-fronto-frontal electrodes resulted in significant differences between large- and small-size problems. We interpreted this as a differential selection of strategy (retrieval vs. procedural strategies) to be

employed in the two problem sizes. ERD was very pronounced in upper alpha at occipito-parietal electrode locations resulting in a bilateral with a more left tendency significant difference. We interpreted this as representing strategy execution and memory retrieval or quantity manipulations. The type of strategy selected/employed significantly modulated the latencies of both ERS and ERD components. Conclusions: Selection and execution of strategies during mental arithmetic processing can be captured by oscillatory activity in individually determined alpha bands. Significant: The amplitude of ERS can be used to determine what type of strategy is selected for an arithmetic problem. Key words: Event-related synchronization, Event-related desynchronization, mental arithmetic, problem-size

Disclosures: E.T. Muluh: None. **L. John:** None. **E. Muluh:** None.

Poster

817. Human Memory Processes: Encoding, Retrieval, and Consolidation

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NIMH 5T90DA02268

Title: Memory related theta gamma coupling in human hippocampal CA1 subfield

Authors: *N. TCHEMODANOV[1], A. TITIZ[2], E. MANKIN[2], I. FRIED[2], N. A. SUTHANA[2,3]; [1]Biomed. Engin., [2]Neurosurg., [3]Psychiatry & Biobehavioral Sci., Univ. of California Los Angeles, Los Angeles, CA

Abstract: Growing evidence suggests that coupling between the phase of theta (3-8 Hz) and amplitude of gamma (30–125 Hz), known as phase-amplitude cross frequency coupling (CFC), may play a role in hippocampal-dependent memory [1-4]. The hippocampus consists of smaller subregions CA1-4, dentate gyrus (DG) and subiculum, which show differential roles in learning and memory [5], yet the ability to selectively record from these regions in humans is limited by both recording and imaging technologies. Therefore, whether CFC occurs within human hippocampal subfields and relates to memory is currently unknown. Here we used microwires to record local field potentials (LFPs) from human hippocampal subfields in 5 epilepsy patients implanted with intracranial depth electrodes. LFP activity was recorded while subjects completed

an object recognition task, where they learned novel images (targets) and later identified targets and similar (lure) images as OLD or NEW. Hippocampal CFC was calculated during learning of subsequently recalled images (i.e. target later identified as OLD and lure identified as NEW) compared to missed images where targets were incorrectly identified as new. CFC strength was calculated via modulation indices (M), which were computed using theta (3-8 Hz) phase and high gamma (80–125 Hz) amplitude during the 4 sec period after stimulus onsets and z-scored against 1000 surrogate distributions [1-3, 6]. Microelectrode localization to hippocampal subfields was done via a 3-way registration using postoperative CTs, high-resolution magnetic resonance images (MRI), and whole brain MRI. We found significant theta-gamma coupling in CA1 during learning of subsequently recalled trials (z_{recall} =3.37, p<0.001) but not during missed trials (z_{miss} =1.38, p=0.084). Furthermore, we found a significant difference in CFC strength between recalled and missed conditions (recall>miss, t_{stat} = 4.74, p<0.001). We did not find these effects in CA23DG (recall>miss, t_{stat} = 1.96, p=0.059; z_{recall} =0.41, p=0.34; z_{miss}=-0.086, p=0.53) or subiculum (recall<miss, t_{stat} = -1.3, p=0.21; z_{recall} =-0.02, p=0.51; z_{miss}=0.356, p=0.36). These results suggest a specific role for theta gamma coupling in the human hippocampal CA1 subfield during learning of subsequently recollected items and support the idea that theta gamma coupling is associated with optimal learning in humans. References: 1. Tort AB et al. 2009 PNAS 106:20942-7 2. Canolty RT and Knight RT 2010 Trends Cogn Sci. 14:506-15 3. Canolty RT et al. 2006 Science 313:1626-8 4. Lega B et al. 2014 Cereb Cortex, (In Press) 5. Carr VA et al. 2010 Neuron, 65:298-308 6. Tort AB et al. 2010 J Neurophysiol., 104:1195-210

Disclosures: N. Tchemodanov: None. **A. Titiz:** None. **E. Mankin:** None. **I. Fried:** None. **N.A. Suthana:** None.

Poster

817. Human Memory Processes: Encoding, Retrieval, and Consolidation

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5R01MH062500 NIMH

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Title: Hemispheric differences in short-term relational memory after unilateral temporal lobe resection for epilepsy

Authors: *E. GAGNON, A. J. RYALS, J. L. VOSS;
Northwestern Univ. Feinberg Sch. of Medicin, Chicago, IL

Abstract: Bilateral hippocampal lesions have been shown to disrupt relational memory performance across even brief retention intervals (seconds). In a previous test of spatial reconstruction for arrays of 2-5 objects with 3-second retention intervals, hippocampal amnesics have shown a disproportionate tendency to commit "swap errors." These errors involve switching the relative positions of objects during array reconstruction, as opposed to purely spatial errors such as increased distance between locations of studied items and reconstructed items. However, little is know regarding effects of lesion hemisphere on spatial versus relational errors. In the present study, we measured reconstruction ability in individuals who had undergone unilateral temporal lobe resection for intractable epilepsy. Participants learned and reconstructed five-item arrays containing either namable objects or novel abstract shapes, with retention intervals of several seconds. Reconstruction errors of interest included swap errors, reflecting relational memory, as well as several spatial memory measures (item misplacement, edge resizing, and item rearrangement). As expected, participants exhibited significantly more errors for reconstructions of novel-shape compared to familiar-object arrays. Individuals with right-lateralized lesions tended to make more memory errors than individuals with left-lateralized lesions, without marked distinction between swap errors specifically and more general spatial memory errors. These preliminary findings are consistent with a greater role of right than left hippocampus in spatial memory, without striking evidence for hemispheric differences in relational memory. Comparisons of performance for lesion subjects with matched healthy controls will also be discussed.

Disclosures: **E. Gagnon:** None. **A.J. Ryals:** None. **J.L. Voss:** None.

Poster

817. Human Memory Processes: Encoding, Retrieval, and Consolidation

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Topic: F.01. Human Cognition and Behavior

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Title: An ECoG study of neural correlates of music listening and recall

Authors: Y. DING[1], Y. ZHANG[1], J. HUANG[4], W. ZHOU[2], Z. LIN[5], B. HONG[1], *X. WANG[6,3];
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Abstract: Previous neural imaging studies have shown that the perception and retrieval of musical information are associated with activations of overlapped brain regions, including inferior frontal lobe, supplementary motor area, premotor cortex, superior temporal gyrus and supra-marginal areas. However, little is known about how the network of brain areas dynamically represents the time course of listening and recall of musical pieces and how the activations of specific brain areas are related to particular musical information. To explore cortical activity patterns associated with music listening and recall, we recorded electrocorticography (ECoG) from Chinese-speaking epilepsy patients with implanted subdural electrode arrays while they were listening to or imagining familiar musical melodies without lyrics. Subjects were asked to first listen to the initial segment of a familiar music piece and then complete the rest of the piece (2 or 5s) by auditory imagery. Subjects indicated the completion of the imagery by pressing a response button. We analyzed the neural activities of the onset phase (0-500ms) and the sustained phase (after 500ms) of music listening and recall separately. For the onset phase, we observed different sequential delay orders of neural activities between music listening and recall. Initialization of the onset cortical activity related to music listening first happened in posterior temporal lobe and supra-marginal area, followed by middle temporal and pre-central areas, and finally reached frontal lobe. In comparison, the cortical activity related to the onset of music recall first appeared in frontal lobe, followed by pre-central area and reached temporal lobe at last, showing a reversed sequential order. For cortical responses of the sustained phase, more brain regions were activated than during the onset phase, with dispersed brain regions activated in both music listening and recall including bilateral pre-central, supra-marginal area, left superior frontal lobe, and right anterior temporal lobe. During the sustained phase, the left temporal lobe and bilateral inferior frontal lobe were mainly involved in music listening, whereas the right superior frontal and superior temporal lobe were mainly involved in music recall. In addition, we found that high gamma band ECoG signal dynamically tracked the music intensity envelope in bilateral posterior superior temporal gyrus during music listening and in bilateral superior frontal lobe during music recall.

Disclosures: **Y. Ding:** None. **Y. Zhang:** None. **J. Huang:** None. **W. Zhou:** None. **Z. Lin:** None. **B. Hong:** None. **X. Wang:** None.

Poster

817. Human Memory Processes: Encoding, Retrieval, and Consolidation

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Topic: F.01. Human Cognition and Behavior

Support: 1R01NS089729

Title: Reducing interference between overlapping memories

Authors: *A. J. CHANALES, B. A. KUHL;
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Abstract: Memories for past events will often share overlapping features. This overlap can lead to interference during memory retrieval, which has long been established as a powerful contributor to forgetting. Although the negative effects of interference are experienced during retrieval, the way in which experiences are encoded is likely to influence the degree to which interference occurs at retrieval. In particular, by forming across-event associations (event integration), interference effects at retrieval may be dramatically reduced or even eliminated (Anderson and McCulloch, 1999). We developed a behavioral paradigm to measure the degree to which overlapping events interfered with one another during memory retrieval. We then considered how various behavioral learning manipulations and neural encoding factors influenced expressions of interference at retrieval. In our paradigm participants initially learned to associate words with pictures of either a face, scene, or object (A-B learning). During a subsequent learning phase (A-C learning), all of the previously learned words (A) were paired with new pictures (C). Memory for the new associations (A-C) was then tested in the presence or absence of an explicit reminder of the B image. Specifically, A-C recall trials were preceded by a briefly presented (200 ms) image that was either (1) the corresponding B image, (2) a novel image from the same category as the B image, or (3) a phase scrambled version of the B image. We found that reminding participants of the B image (i.e., an overlapping memory) interfered with retrieval of the C associate as reflected by reduced recall accuracy and longer reaction times relative to control conditions. Having established a reliable interference effect, we ran a modified version of the paradigm to test whether reminding subjects of the A-B association during A-C learning would influence interference effects at retrieval. Indeed, this manipulation to A-C learning eliminated the ‘cost’ of presenting the B item during A-C retrieval. In other words, when A-B and A-C associations were learned together, interference between B and C items at retrieval was eliminated. Finally, we ran an fMRI study to test whether spontaneous reactivation

of older associations (B items) during A-C learning predicted the degree of interference between B and C items during A-C retrieval.

Disclosures: **A.J. Chanales:** None. **B.A. Kuhl:** None.

Poster

817. Human Memory Processes: Encoding, Retrieval, and Consolidation

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Topic: F.01. Human Cognition and Behavior

Title: Episodic memory updating facilitated by sleep after reactivation and new learning

Authors: ***N. BRYANT**, L. NADEL, R. L. GOMEZ;
Psychology, The Univ. of Arizona, Tucson, AZ

Abstract: A growing body of evidence suggests that memories are not fixed entities; instead, an old memory can be reactivated, updated with a different experience, and reconsolidated to include both the old and new information. Furthermore, updating of previously-consolidated memories with novel experiences appears to be a time-dependent process, which may implicate offline memory processes occurring during sleep. Sleep-dependent memory processes have been investigated within the framework of consolidation in general, as well as procedural memory updating in particular; however, the role of sleep in episodic memory reconsolidation remains unexplored. Given that sleep has been shown to facilitate veridical episodic memory, it could also play a role in the updating and reconsolidation of old representations with new learning. We tracked the sleep of 25 undergraduates using accelerometers and daily sleep diaries during a week of testing using the reconsolidation paradigm. In this paradigm, subjects learn two sets of objects separated by 48 hours (Sets 1 and 2). Before learning the second set, participants are reminded of the first learning experience (reactivation). At test 48 hours later, subjects are assessed on their memory for the objects and the day on which they were learned. Previous work has implicated the reminder in greater attribution of Set 2 objects to the Set 1 memory (intrusions) than Set 1 objects to the Set 2 memory (errors), demonstrating reconsolidation of the old memory with the new items. The current study found amount of sleep is significantly associated with intrusions $R2=.34$, $F(2,22)=5.75$, $p<.01$. In particular, less sleep after learning Set 1 ($\beta=-.52$, $p<.05$) and more sleep after learning Set 2 ($\beta=.52$, $p<.05$) predicts the number of Set 2 objects attributed to Set 1. However, no relationships were found between sleep amount and errors, or Set 1 items misattributed to Set 2. Our results mirror prior findings that memory consolidation is benefitted by a night of sleep; however, in this case sleep enhanced

reconsolidation of a prior memory with new learning. Interestingly, the opposite effect was observed after learning Set 1, such that getting less sleep after learning increased updating. These results imply that memories that are not fully consolidated by a night of sleep are perhaps "weaker," and thus more susceptible to reactivation and updating. Importantly, sleep was not related to errors in the other direction, or misattribution of old items to the new experience. The next phase of this research will use electroencephalography to investigate sleep-dependent brain mechanisms underlying memory reconsolidation.

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Poster

817. Human Memory Processes: Encoding, Retrieval, and Consolidation

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Program#/Poster#: 817.10/AA25

Topic: F.01. Human Cognition and Behavior

Support: KAKEN

Title: Change in effects of odor contexts over time that modify mental timeline in relation to the order of remote and recent past episodes

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Abstract: Humans often have an incorrect impression from memory that they might have experienced past events a moment or a long ago that had occurred years or minutes ago in real world, when they are currently under the situations the same as or different from ones in which these events had really occurred. Thus contexts which consist of background of situations can modify order of past events in memory representations in respect to which events preceded or followed. Memories are dynamically altered over hours or days. Whether contextual effects on memory in respect to order of past events would change over time is unknown. Here, we demonstrated different effects of context on order of past events in memory immediately and hours after end of events. Young, adult, healthy volunteers participated in this study. Different lists of English words were visually presented in two sessions separated by a 10-min interval. While subjects judged whether presented words belonged to living or nonliving things, different odors were administrated in each session. After one or 6 hours delay, subjects were asked to

choose which words were presented in the second session (i.e. recent past) or in the first session (i.e. remote past), under conditions in which odors the same as ones exposed in the first or second session, or different new ones (i.e. control) were administrated. Performance errors were measured in three odor contexts. At one hour, subjects made more incorrect responses that they might have seen words in the second session (i.e. recent past) that were physically presented in the first session (i.e. remote past) when the same odor conditions as ones exposed in the first session were applied, compared with other two contexts. At 6 hours, subjects made more incorrect responses to recall that they might have seen words in the first session (i.e. remote past) that were physically presented in the second session (i.e. recent past) when the same odor conditions as ones exposed in the second session were applied, compared with two other contexts. These results revealed different effects of odor contexts on memory in respect to order of past events at 1 hr and 6 hr time points. We conclude that effects of odor contexts on memory in respect to order of past events dynamically change, probably through progressive processes of memory formation.

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Poster

817. Human Memory Processes: Encoding, Retrieval, and Consolidation

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Topic: F.01. Human Cognition and Behavior

Support: NSF GRFP

R01 MH 076492

Title: How does consolidation influence neural and behavioral integration?

Authors: ***A. TOMPARY**, L. DAVACHI;
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Abstract: Systems-level consolidation is theorized as the transfer of neural traces of episodic memories from the hippocampus to distributed cortical regions over time. This distribution is thought to rely on the repeated extraction of information from hippocampus to cortex, a mechanism that may be well suited to facilitate the integration of memories with shared information. However, little research to date has studied how consolidation influences the neural integration of memory traces and how this relates to behavior. We developed a two-day fMRI

study to test whether memories of objects in overlapping sequences would become more behaviorally integrated over time, and how changes in memory representations might reflect this integration. Each day, subjects incidentally learned a different set of objects presented in a continuous sequence. The sequences were ordered such that some objects were always preceded by the same sequence of two objects. Immediately after the day 2 encoding session, participants completed a recognition memory test with objects from both encoding sessions. Critically, trials were ordered such that we could test for the integration of objects in overlapping sequences via priming. Preliminary behavioral data show that recognition of an object was faster when preceded by successful recognition of an object studied in an overlapping sequence. Importantly, this priming benefit only emerged for objects learned 24 hours prior to the test. These initial results suggest that consolidation might enhance the integration of memory representations with overlapping information. Planned fMRI analyses will employ pattern similarity to characterize how consolidation influences memory representations related to behavioral measures of integration.

Disclosures: **A. Tompary:** None. **L. Davachi:** None.

Poster

817. Human Memory Processes: Encoding, Retrieval, and Consolidation

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 817.12/AA27

Topic: F.01. Human Cognition and Behavior

Support: A*STAR JCO Grant #1335h00098

Title: Neural pattern similarity between encoding and retrieval correlates with memory-based visual task performance

Authors: ***S. OH**[1], K.-H. CHUANG[1], C. TAN[2], P.-J. HSIEH[3];
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Abstract: The current study examined which cortical areas correlate with behavioral performance in a memory-based task, using functional magnetic resonance imaging (fMRI) and representational similarity analysis (RSA). Specifically, we tested if pattern similarity between encoding and retrieval correlate positively with memory-based task performance. Participants performed encoding and retrieval tasks for the same set of visual objects. The activation patterns for each of the visual objects were extracted separately from encoding and retrieval task sessions.

The activation pattern similarities between the two task sessions were then calculated for each of the visual objects. The results showed that the degree of neural pattern similarity between encoding and retrieval sessions in multiple brain areas correlates positively with subsequent memory-based task performance for the studied visual objects. The brain areas that showed the positive correlation include areas in medial temporal cortex, superior parietal cortex, and prefrontal cortex.

Disclosures: **S. Oh:** None. **K. Chuang:** None. **C. Tan:** None. **P. Hsieh:** None.

Poster

817. Human Memory Processes: Encoding, Retrieval, and Consolidation

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Topic: F.01. Human Cognition and Behavior

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NIH R01 EY021755

Title: Reinstating mental context with closed-loop neurofeedback

Authors: ***M. T. DEBETTENCOURT**, N. B. TURK-BROWNE, K. A. NORMAN; Princeton Univ., Princeton, NJ

Abstract: Prior work has shown that reinstating contextual information during to memory retrieval benefits recall performance (for a review, see Manning, Kahana, & Norman, 2014). In this study, we sought to investigate how contextual reinstatement can be enhanced, with the goal of improving recall. During a real-time fMRI session, participants completed multiple runs of a memory task. Each run was subdivided into three phases: study, neurofeedback, and recall. During the study phase, participants studied lists of words with photographs (e.g. scenes) interleaved between the words as context. After encoding the words into memory, participants were briefly distracted to prevent them from rehearsing items or their contexts. Then, participants were cued to start reinstating the context from the lists - that is, to think back to the photographs that had been presented during that list (e.g., to reinstate the scenes from a list with scene photographs). During this time, we applied a multivariate pattern classifier trained on voxels in the temporal lobe to decode whether they were reinstating photographs from the correct category. To help participants reinstate the correct context, we provided them with feedback

based on the output of the classifier, which reflected how strongly the correct category was represented in their brain. For feedback purposes, the participant was presented with a series of composite photographs (e.g. face/scene), and the proportions of the image categories in the mixture were manipulated. If the classifier outputs suggested they were reinstating the correct category, then the proportion of this category in the mixture increased. In other words, the stimuli were used to externalize our measures of the participant's internal context, in turn biasing subsequent internal processing in a helpful direction. If they were reinstating the incorrect category, the feedback served to provide an error signal, helping participants redirect their reinstatement. After this neurofeedback, participants were probed to freely recall as many items as possible from one of the lists. In the "valid" condition, they were probed to report the words from the list whose context they reinstated. In the "invalid" condition, they were probed to report the words from another list. Overall, memory was better on valid tests, consistent with the idea that contextual reinstatement boosts recall. Moreover, the more that participants were able to reinstate the context during neurofeedback, as indicated by classifier output, the more words were recalled. Future control experiments will explore the specific role of neurofeedback in fostering contextual reinstatement.

Disclosures: M.T. deBettencourt: None. **N.B. Turk-Browne:** None. **K.A. Norman:** None.

Poster

817. Human Memory Processes: Encoding, Retrieval, and Consolidation

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 817.14/AA29

Topic: F.01. Human Cognition and Behavior

Title: Enhancement of numerical processing by combining phase coupled transcranial alternating current stimulation and training

Authors: *A. LEBEDEVA[1], R. COHEN KADOSH[2], H. ARSLANKOÇ[1], M. FEURRA[1]; [1]Natl. Res. Univ. Higher Sch. of Econ, Moscow, Russian Federation; [2]Univ. of Oxford, Oxford, United Kingdom

Abstract: Cognitive training is undoubtedly efficient for improving arithmetical skills, but it is more effective when coupled with brain stimulation. We coupled training with brain stimulation in the form of Transcranial Alternating Current Stimulation (tACS), a noninvasive technique that modulates neural activity. Our study involved subjects who were trained for 3 consecutive days by using simple and hard arithmetical problems. At first all participants underwent pretest to evaluate their initial performance. Then they were divided into 4 groups: theta phase coupled

stimulation, theta anti-phase coupled stimulation, gamma phase-coupled stimulation and sham group. We showed that theta phase-coupled stimulation group had a robust improvement in terms of reaction times and ability to use retrieval strategy with respect to all other groups. Moreover, our subjects not only performed better in every day trained tasks , but also in untrained tasks, by showing transfer of cognitive skills to untrained problems. This evidence proves that phase coupled tACS may be used to modulate a cortical network, by inducing frequency specific improvement that lead to learning effects.

Disclosures: A. Lebedeva: None. **R. Cohen Kadosh:** None. **H. Arslankoç:** None. **M. Feurra:** None.

Poster

817. Human Memory Processes: Encoding, Retrieval, and Consolidation

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Support: NSF GRFP

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Title: Features of sleep architecture relate to the neural representation and behavioral stability of memories

Authors: *E. COWAN[1], A. LIU[2,3], S. KOTHARE[2,3], O. DEVINSKY[2,3], L. DAVACHI[1,4]; [1]Ctr. For Neural Science/ New York Univ., New York, NY; [2]Langone Sch. of Med., [3]Comprehensive Epilepsy Ctr., [4]Dept. of Psychology, New York Univ., New York, NY

Abstract: Theories of systems memory consolidation posit that memories are stabilized as they become more distributed throughout the cortex. Sleep has been linked with successful memory consolidation, and evidence suggests particular features in the architecture of sleep may relate to sleep-dependent memory enhancements. Recent evidence suggests a 24-hour delay promotes more distributed memory traces, as measured by hippocampal-cortical functional connectivity, in

manner predictive of subsequent behavioral resistance to forgetting, indicating a specific role in memory stabilization. However, it remains unknown what aspects of sleep architecture are related to the distribution of memory traces, and the effect this has on behavioral measures of memory. To investigate this relationship, we designed a three-day experiment utilizing overnight measurements of polysomnography, fMRI, and behavior. Subjects were asked to repeatedly encode sets of word-image pairs with an intervening period of overnight sleep (Sleep List), or a brief wakeful period (Awake List), thus differing in the opportunity for potential consolidation. During the second presentation, subjects restudied the previously seen word-image pairs while in the scanner. Cued source recall was probed immediately following the scan and after a 24-hour delay, providing a measure of memory stability over time. Overnight sleep was classified into its component stages, revealing a selective relationship between duration of Stage 2 sleep and memory performance for the delayed test. Analysis of the fMRI data demonstrated a positive correlation between duration of Stage 2 sleep and univariate activity in ventromedial prefrontal cortex (vmPFC), left middle occipital gyrus, and left lateral occipital cortex, but a negative correlation with activity in the hippocampus, perirhinal and parahippocampal cortices, specifically for the successfully recalled Sleep List pairs. These findings suggest that the duration of Stage 2 sleep relates to a shift in activation patterns from medial temporal lobe regions to distributed cortical regions. Furthermore, activity in the vmPFC and left middle occipital gyrus regions was found to significantly correlate with memory performance only on the delayed test, indicating that activity in these regions may relate to the stability of the memory. Additional analyses will focus on the relationship of other oscillatory features of sleep architecture, including spindle density, with the neural representation and behavioral expression of memory traces.

Disclosures: **E. Cowan:** None. **A. Liu:** None. **S. Kothare:** None. **O. Devinsky:** None. **L. Davachi:** None.

Poster

817. Human Memory Processes: Encoding, Retrieval, and Consolidation

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Program#/Poster#: 817.16/AA31

Topic: F.01. Human Cognition and Behavior

Title: Intrusions in episodic memory: reconsolidation or interference?

Authors: *T. SOMMER[1], A. KLINGMÜLLER[1], J. B. CAPLAN[2];
[1]Univ. Med. Col. Hamburg Eppendorf, Hamburg, Germany; [2]Psychology Dept., Univ. of Alberta, Edmonton, AB, Canada

Abstract: It would be profoundly important if one could extend reconsolidation research in animals and in other memory domains to human episodic memory. Here we examine a procedure based on free recall of objects, with a contextual reminder cue (the testing room), that has been rallied to support the notion of reconsolidation in human episodic memory (Hupbach et al., 2007). We found that replication is not straight-forward, even when matching performance-level with prior studies (Experiment 1), which raises questions about the generality of the effect. Experiment 2 included two manipulations that pitted predictions of the reconsolidation account against accounts based on interference theory. Experiment 3 examined the effect of familiarity, or salience of the testing context. Using a highly unusual testing room as context, we were able to replicate the original findings to a certain degree. Finally, experiment 4 tested whether retrieval (followed by re-encoding) might occur at all during re-exposure to the context in the absence of interfering new learning, a critical assumption of the reconsolidation account. The pattern of findings across these experiments poses serious challenges for the reconsolidation account, and may be accommodated by alternative accounts that do not assume consolidation or reconsolidation, but instead, explain behavior in terms of the two lists interfering with one another during retrieval (Sederberg et al., 2011; Gisquet-Verrier and Riccio, 2012). References Gisquet-Verrier P, Riccio DC (2012) Memory reactivation effects independent of reconsolidation. Learn Mem Cold Spring Harb N 19:401-409. Hupbach A, Gomez R, Hardt O, Nadel L (2007) Reconsolidation of episodic memories: a subtle reminder triggers integration of new information. Learn Mem 14:47-53. Sederberg PB, Gershman SJ, Polyn SM, Norman KA (2011) Human memory reconsolidation can be explained using the temporal context model. Psychon Bull Rev 18:455-468.

Disclosures: T. Sommer: None. **A. Klingmüller:** None. **J.B. Caplan:** None.

Poster

817. Human Memory Processes: Encoding, Retrieval, and Consolidation

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Topic: F.01. Human Cognition and Behavior

Support: NIH Grant R01 MH100121

Title: Schema representations in hippocampus and medial prefrontal cortex support generalization in novel contexts

Authors: *R. MOLITOR[1], M. L. SCHLICHTING[1], M. L. MACK[1], K. F. GUARINO[1], S. MCKENZIE[2], H. EICHENBAUM[3], A. R. PRESTON[1];
[1]Univ. of Texas At Austin, Austin, TX; [2]New York Univ., New York, NY; [3]Boston Univ., Boston, MA

Abstract: Past experience often influences how we learn new information. Recent work suggests that existing memories can benefit new learning by providing a knowledge framework-or schema-into which new information can be integrated. For instance, rodent electrophysiology has shown that the hippocampus forms schematic representations of task structures that support both learning of related information and generalization to overlapping contexts. In contrast, evidence of schemas in human hippocampus has only been indirect. Neuroimaging studies have found increased activation in hippocampus, as well as medial prefrontal cortex (mPFC), during encoding of events that overlap with prior knowledge. While such findings indicate that these regions support encoding of events that relate to existing memories, they say nothing about the underlying structure of the encoded representations or how they are applied in new contexts. Here, we used pattern similarity analysis (PSA) to quantify hippocampal and mPFC representations of a well-learned task structure to determine whether such schemas are reactivated in novel contexts to support generalization. During fMRI scanning, participants learned which of two objects (e.g., A or B; C or D) was rewarded in two spatial contexts (C1 and C2). The correct choice was determined by a rule contingent on spatial context, such that an object rewarded in one context (e.g., C1: A+/B-) was not rewarded in the other context (i.e., C2: A-/B+). Training on the contextual rules was followed by a transfer task with two novel spatial contexts (C3 and C4). Critically, the rule structure overlapped between training and transfer, such that an object rewarded in one training context (e.g., C1: A+/B-) was also rewarded in a corresponding transfer context (i.e., C3: A+/B-). Using PSA, we calculated the neural similarity between each object, reward valence, and spatial context to create a correlational structure characterizing hippocampal and mPFC schemas formed during training. We compared these schemas to the same correlation matrix derived from hippocampal and mPFC activation patterns during transfer. We found that hippocampal and mPFC correlational structures were preserved from training to transfer, consistent with the application of the learned task schema to the new contexts. This finding suggests that generalization of contextual rules to novel events is supported by reactivation of hippocampal and mPFC schemas. By quantifying activation patterns according to task structure, the present approach provides a direct means of measuring schemas in the human brain and offers unique insight into how prior knowledge guides learning in new situations.

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Poster

817. Human Memory Processes: Encoding, Retrieval, and Consolidation

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Topic: F.01. Human Cognition and Behavior

Support: NIH P50 MH094263

Title: Examining the differential course of rule learning using a Bayesian learning approach

Authors: *A. E. CHANG[1], A. S. WHITEMAN[1], A. JOHNSON[2], C. E. STERN[1];
[1]Ctr. for Memory and Brain, Boston Univ., Boston, MA; [2]Psychology, Bethel Univ., St. Paul, MN

Abstract: This study sought to understand individual differences in context-dependent rule learning. We developed a context-dependent rule learning task in which object pairs were presented in one of four quadrants (spatial context locations) on a screen. Participants learned to associate different object pairs with spatial context through trial and error. We tested two experimental conditions in which we varied stimulus presentation order. In the object oriented condition (N = 34), the associations for one object were shown across 4 spatial locations before the associations for another object. In the spatial oriented condition (N = 37), the associations for all objects were shown in 1 spatial location before the associations for a different spatial location. To analyze the data, we created learning curves (Gallistel et al. 2004, PNAS; Smith et al. 2004, J.Neuro), and used a Bayesian learning approach (Johnson et al. 2014, SFN) to examine the progression of hypotheses participants might be testing as they gradually learned the task. The results suggest participants acquired the correct task rules more quickly in the object oriented training condition than the spatial oriented training condition. The Bayesian learning analysis showed that while each of the training conditions resulted in the correct task representations by the end of training, the probability of the correct representation developed earlier and better predicted trial outcomes in the object training condition. We also examined the effects different priors had on inference in our Bayesian learning approach. Specifically, we used flat priors to simulate naïve learning, and U-shaped priors to express the idea that participants could be testing more systematic, elegant hypotheses about the task rules as they learn (i.e. that a candidate rule either always holds or it never holds). While under the naïve learning model, behavior was consistent simply with identification of the correct task representation; under the U-shaped prior model, behavior was more consistent with participants sequentially testing different possible rules. A preliminary analysis of reaction times, however, suggested that the flat prior model might account for learning marginally better than the hypothesis-testing prior across our sample.

This approach provides an intriguing framework to examine the differential course of rule learning representations and corresponding neural substrates within single individuals.

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Poster

817. Human Memory Processes: Encoding, Retrieval, and Consolidation

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Topic: F.01. Human Cognition and Behavior

Support: NIH R00AG036845

Title: Pattern separation of systematically similar stimuli during delayed matching to sample

Authors: ***R. K. NAUER**[1,2], M. F. DUNNE[3], A. S. WHITEMAN[1,2], C. E. STERN[1,2], K. SCHON[1,2,3];
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Abstract: Pattern separation is a putative computational process to orthogonalize overlapping stimuli. Previous neuroimaging studies in humans have demonstrated that hippocampal subregions DG/CA3 are critical for successful pattern separation (Bakker et al., 2008). Tests of long-term memory (LTM) and working memory (WM) have found increased DG/CA3 and CA1 activity during encoding may support pattern separation (Carr et al., 2010) while other areas in the medial temporal lobes (MTL) including subiculum, entorhinal cortex (EC) and CA1 maintain highly similar representations during a WM task (Newmark et al., 2013; Nauer et al., 2015). Here, we extend these studies by parametrically varying the level of stimulus similarity in the context of a WM task. We hypothesized that the degree of stimulus overlap would drive recruitment of MTL areas, and that high similarity levels would negatively modulate task accuracy. Participants performed a delayed-matching to sample (DMS) task during high-resolution fMRI optimized for examining MTL cortex and hippocampal subfield contributions. Stimuli consisted of gray scale images of human faces. For each trial, two sample stimuli were shown in succession (2 s each), followed by a delay (10 s), followed lastly by a test stimulus (2 s). Participants were asked to judge whether the test face was a match to the first sample face or the second sample face, or was a nonmatch. Critically, similarity of the face stimuli was systematically varied by trial. Each trial belonged to one of three conditions: low similarity (10%

stimulus overlap), medium similarity (30% stimulus overlap), or high similarity (50% stimulus overlap). Regions of interest (ROIs) included EC, perirhinal cortex, parahippocampal cortex, and hippocampal subfields (CA1, DG/CA3, subiculum). Behavioral analysis (N=24) of accuracy showed a negative main effect of stimulus similarity, denoting accuracy decreased as similarity increased. Importantly, accuracy was above chance for all similarity levels indicating subjects were able to disambiguate stimuli successfully. Additionally, we found an interaction between similarity and trial type such that similarity had a greater negative impact on accuracy for nonmatch trials. These results suggest that participants are able to disambiguate varying degrees of overlapping stimuli and lead us to hypothesize that successful disambiguation during WM may be supported by the same putative pattern separation mechanisms that have been demonstrated in LTM. Ongoing functional neuroimaging data analysis is focused on the contributions of ROIs during the components of the DMS task related to accuracy and the degree of stimuli similarity.

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Poster

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Support: NIH Grant R01MH097061

Title: Resolving the paradox of mixed positive and negative correlations between confidence and accuracy in memory

Authors: *P. MASSET, A. KEPECS;
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Abstract: The capacity to learn and recall previously encountered objects or situations are central to adaptive behavior at timescales beyond those of sensory systems. The ability to know when to trust recalled memories and when to doubt them allows us to make plans about current and future actions. Although the ability to assign appropriate level of confidence to recalled memories confers an obvious evolutionary advantage but the accuracy of such confidence reports has been questioned in the literature. Some studies have reported strong correlations between confidence and recall accuracy while others have found no or even negative correlations. Here

we present a model that addresses this paradox. We specifically consider results from experiments revealing that confidence is positively correlated with recall accuracy for correct identifications but is negatively correlated for false identification of distractors. We present a statistical explanation and an implementation inspired by signal detection theory to show that the presence of negative correlations is expected when categorizing the data according to properties only available to the experimenter. Memories (targets or distractors) are assumed to be encoded along a decision axis with a decision boundary separating the two categories. Memories generate percepts on this axis that are sampled from a distribution as a result of noise induced during memory formation and recall. Subjects categorize the percepts according to their position with respect to the decision boundary. The reported confidence is a monotonic function of the distance of the percept from the decision boundary. We demonstrate that this simple model can account for the paradoxical correlation structure of confidence and we fit it to previously published data. Within this framework, the negative correlations suggest that the individual subjects share a common discriminability measure across the population. We discuss the potential societal applications our predictions such as improved behavioral designs to evaluate the veridicality of confidence reports in eyewitness testimony.

Disclosures: **P. Masset:** None. **A. Kepecs:** None.

Poster

817. Human Memory Processes: Encoding, Retrieval, and Consolidation

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Program#/Poster#: 817.21/AA36

Topic: F.01. Human Cognition and Behavior

Title: False memories are associated with the reactivation of conceptual gist-related information

Authors: *E. A. WING[1], B. R. GEIB[2], R. CABEZA[2];
[1]Dept. of Psychology & Neurosci., [2]Duke Univ., Durham, NC

Abstract: Although long term memory can support vast amounts of information in great detail, memory processes sometimes give rise to the retrieval of inaccurate or false information. In some instances, false memories are thought to be driven by the formation of an overall conceptual gist that makes discrimination amongst similar items difficult. This process may account for effects in the well-known Deese-Roediger-McDermott (DRM) paradigm, in which subjects encode lists of words strongly related to a specific (but unpresented) critical item, and are then more likely to falsely report having studied that critical item at test. Despite numerous investigations using this paradigm, there is surprisingly little neuroimaging evidence linking

false memories to the reinstatement of distributed gist-level information from encoding. To address this issue, we first compared the distributed pattern similarity for items pairs from the same lists to the similarity of between-list pairs. Greater similarity for within-list pairs was evident in left ventrolateral prefrontal cortex (VLPFC) and posterior midline, indicating that these regions are sensitive to semantic content. Importantly, the left VLPFC also showed greater similarity for cross-phase comparisons between encoding and critical false alarms, in contrast to matched correct rejections. These results offer initial evidence that false memories are driven by the reinstatement of conceptually-related gist information.

Disclosures: **E.A. Wing:** None. **B.R. Geib:** None. **R. Cabeza:** None.

Poster

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Topic: F.01. Human Cognition and Behavior

Support: UNAM PAPIIT IN304112

Title: Output format - as well as input format - significantly influences performance in a free-recall multiple trial task

Authors: *V. M. SOLIS, SR;
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Abstract: Several hypermnesia studies (incremental net recall across trials) illustrate how different input formats modify performance. Words, pictures, and Socratic stimuli (dictionary-like definitions) are respectively better remembered, and words are not generally hypermnesic. An interesting question is whether output format may influence memory performance. Dragone, Brown, Krane & Krane (1980) asked that question and crossed factorially input (pictures or words) with output format (also pictures or words). Levels of cumulative recall showed higher picture recall and higher recall across trials, but they reported cumulative recall, which invariably grows across trials. Our objectives are: To examine free-recall for words and pictures across 3 trials by factorially combining input (pictures or words), with output format (also pictures or words) and to assess net recall. Method Participants. 99 freshmen, Psychology Department, University of Mexico allocated to four groups. Materials. 40 concrete, frequent concepts presented either as words or pictures. Pictorial stimuli from Snodgrass & Vanderwart´s (1980) standardised list. Design. Mixed factorial 2 x 2 x 3. Input and output format varied between-

participant, 3 free-recall trials (R1, R2, R3) varied within-participant. Procedure. Participants tested in groups. Presentation rate: 5 s/stimulus; inter-stimulus interval: 1 s. A 3-min distractor task was followed by R1. There were 2 ten-min inter-trial intervals. Results Word-word group. Net recall grew significantly across trials, $F(2, 46) = 14.41$, $p < .0001$, $\eta p2 = .39$. Pairwise comparisons tests show no differences between R1 and R2, and significant R2-R3 and R1-R3 differences, $p < .001$. Word-picture group. Hypermnesia is even higher in this group, $F(2, 46) = 70.26$, $p < .00001$, $\eta p2 = .75$. Pairwise comparisons tests show highly significant differences among trials, $p < .001$; the same pattern occurred in the remaining groups and is not reported separately. Picture-word group. This group also shows highly significant hypermnesia, $F(2, 50) = 49.49$, $p < .0001$, $\eta p2 = .66$. Picture-picture group. Hypermnesia also emerged in this condition but with the highest levels of significance and of associative strength, $F(2, 48) = 227.39$, $p < .000001$, $\eta p2 = .91$. Discussion Output format seems to influence performance. We explored the contribution of input and output formats while maintaining other relevant factors constant. Our study suggests that, together with input format, output format may be an important factor in memory tasks. These results add to the extant literature on hypermnesia and also suggest some useful strategies to plan educational and training programmes.

Disclosures: **V.M. Solis:** None.

Poster

818. Human Cognition and Behavior: Attentional Networks

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Support: NIH F32 NS090757

NIH R01 NS079698

Title: Functional organization of the human thalamus and thalamocortical connectivity estimated by intrinsic functional connectivity

Authors: *K. HWANG[1], M. BERTOLERO[2], M. D'ESPOSITO[1];
[1]Helen Wills Neurosci. Inst., Univ. of California Berkeley, Berkeley, CA; [2]Psychology, Univ. of California Berkeley, Berkeely, CA

Abstract: The thalamus relays information from peripheral sensory organs to the cerebral cortex, and may also mediate the exchange of information between cortical regions. Functional

interactions between the thalamus and cerebral cortex is therefore a critical component of brain network functions. Previous resting-state functional connectivity fMRI (rs-fcMRI) and diffusion imaging MRI studies have identified thalamic subdivisions that are preferentially connected with each cerebral lobe. Recent rs-fcMRI studies however indicate that cerebral functional networks are not confined to the anatomical division of cerebral lobes. Thus, it is unclear how thalamocortical pathways contribute to this distributed cortical network organization. To answer this question, we analyzed a large-sample of high-resolution resting-state fMRI data from the Human Connectome Project and the Brain Genomics Superstruct Study. Data from 568 human participants were included. We first applied a graph-theoretic modularity detection algorithm to identify cortical functional networks. Replicating previous studies, several distributed cortical networks were identified, each corresponding to a putative functional system. We then mapped the correlation between each thalamic voxel and each cortical functional network, and assigned each thalamic voxel to its most strongly correlated cortical network. Our approach revealed a symmetric and well organized topography of thalamic parcellation. This parcellation included (1) a ventral medial subdivision linked to the somatomotor network, (2) a posterior inferior subdivision linked to the visual network (3), an anterior subdivision linked to cingulo-opercular network, (4) a mediodorsal subdivision linked to the frontoparietal cognitive control network, and (5) a posterior superior subdivision linked to the dorsal-attention network. The parcellated thalamic subdivisions were then included as separate regions of interests for further whole-brain graph analysis. Consistent with the identified topography, thalamic subdivisions linked to fronto-parietal networks, which contain many connector hubs, also were identified as connector hubs. Connector hubs are nodes with diverse connections across networks. This pattern of thalamic organization suggests that in addition to unimodal sensory processing, the thalamus likely contributes to integrative heteromodal information processing.

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Poster

818. Human Cognition and Behavior: Attentional Networks

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Topic: F.01. Human Cognition and Behavior

Support: NIH Grant R01 MH094305

Title: Dissociable functional connectivity of the frontal eye field for overt and covert shifts of attention

Authors: *M.-A. MACKIE[1], T. WU[2], P. R. HOF[3], J. FAN[2,4];
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Abstract: It is well understood that the orienting of attention can be employed via overt or covert shifts, i.e. with or without eye movements, both accompanied by activation in the frontal eye field (FEF). However, due to the existence of various populations of neurons within the FEF, whether overt and covert shifts of attention rely on the same underlying neural mechanisms remains unclear. In this study, we used tasks to elicit overt and covert shifts of attention in response to both endogenous and exogenous cues, and employed functional magnetic resonance imaging to investigate the functional connectivity of the FEF underlying the two types of shifts. General linear model results replicated previously demonstrated overlap in areas of activation for the two types of shifts, particularly in the FEF. Psychophysiological interaction analyses with the FEF as seed region revealed differential patterns of functional connectivity for the two types of shifts. Compared to covert shifts, overt shifts of attention elicited greater connectivity of the FEF to striate and extrastriate areas, as well areas near and along the intraparietal sulcus. In contrast, compared to the overt shifts, covert shifts elicited greater connectivity of the FEF to superior frontal gyrus and subcortical structures such as superior colliculus and caudate nucleus. These results demonstrate that although there are shared brain regions involved in both overt and covert shifts of attention with the FEF as the key region, the connectivity supporting these two types of orienting are different.

Disclosures: **M. Mackie:** None. **T. Wu:** None. **P.R. Hof:** None. **J. Fan:** None.

Poster

818. Human Cognition and Behavior: Attentional Networks

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Topic: F.01. Human Cognition and Behavior

Support: Wellcome Trust 084067, 091928

Title: Frontal Eye Fields TMS causes visual cortex excitability to phase-align at beta frequency

Authors: *D. VENIERO[1], S. MORAND[1], F. DUECKER[2,3], A. T. SACK[2,3], J. GROSS[1], G. THUT[1];

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Abstract: The human frontal eye fields (FEFs) are a main node of the attentional network. TMS studies have demonstrated that FEFs activation modulates visual cortex excitability, and attention has been shown to phase-align occipital brain rhythms at specific frequency bands. However, the oscillatory nature of changes in visual cortex excitability induced by FEF-TMS has never been examined. To this end, we employed a bifocal Transcranial Magnetic Stimulation (TMS) protocol. The first pulse was used to activate the FEFs projections to visual areas, whereas the second pulse was applied to test the resulting excitability changes in primary visual cortex (V1) or extrastriate cortex (V5) via measuring phosphenes perception as a function of the time delays between the two pulses. If FEFs activation phase-aligns oscillatory activity over the occipital cortex, one would expect a periodicity in phosphenes perception locked to the FEF-TMS pulse. Fifteen participants were enrolled to assess right FEF-right V1 (rFEF-rV1) (8 participants) or rFEF-rV5 (7 participants) interactions at 19 time delays (30 to 300 ms in steps of 15 ms). The specificity of the results to FEF-occipital area interactions was controlled for by means of two additional bifocal TMS conditions (vertex-rV1, vertex-rV5). To test for a cyclical pattern in phosphene perception rate, a curve-fitting procedure was applied fitting all cosine models ranging from 7 to 25 Hz. R-squared values were statistically evaluated using a bootstrapping procedure. For any observed periodicity we tested whether phase consistency across participants could be found, by extracting the phase of the best fitting cosine model for each participant and condition. For the rFEF-rV5 condition, cosine models in the beta-frequency range (from 14-18 Hz) significantly fitted the behavioural data. Notably, when directly testing for a phase locking to the FEFs stimulus, we found significant phase consistency for the beta band (17Hz) in the FEF-V5 condition ($p<0.01$), whereas no significant phase consistency emerged for any frequency in any of the other conditions. In conclusion, FEFs can modulate V5-by changing its excitability over time as revealed by the modulation of TMS-induced phosphene perception. We show that FEFs exert a causal influences over V5 by phase resetting oscillatory activity in the beta band. This is in line with findings suggesting that beta oscillations are mainly involved in top-down interactions within cortical networks.

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Poster

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Program#/Poster#: 818.04/AA41

Topic: F.01. Human Cognition and Behavior

Title: The effect of TMS to the frontal cortex on the relationship between arousal, attention, brain state and behaviour

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Abstract: Introduction: Behavioural performance is related to the attention directed at the task. Over extended periods of time attention naturally waxes and wanes and performance can follow these attentional states. The frontal cortex is thought to contribute substantially to attentive state and has also been implicated in contributing to arousal and autonomic state. It is the purpose of this research to examine how brain state relates to autonomic state, attention and task performance. Methods: We employed counterbalanced transcranial magnetic stimulation (TMS) or sham stimulation to the left frontal cortex in 17 healthy participants before they performed the graduated continuous attention task. During the task, performance, EEG and heart rate were continuously monitored. Results: TMS had no effect on group level reaction time, coefficient of RT, nor did it affect overall errors of commission or omission. However, TMS to the left frontal cortex ameliorated the strong positive relationship between lapse rate and coefficient of RT ($r = 0.71$, $p = 0.001$ to $r = 0.24$, $p = 0.34$). Though TMS did not reduce the group level number of errors of omission or group level coefficient of RT the relationship between the two was severed. This suggests that something has changed and this may be related to arousal and brain state during the task. Examination of heart rate variability (HRV) showed a group level effect of TMS such that TMS increases HRV compared to sham stimulation ($p<0.007$). Analysis of EEG power spectra in frontal and parietal areas revealed TMS to affect the normal brain reaction to hits, misses and false alarms. Finally, analysis within task performance revealed that in general, instances of high coefficient RT are associated with high HRV and an increase in beta/gamma power. Conclusions: The precise relationship between performance, attention, arousal and brain state is not a simple one. However, based on the results of this study, times of high attention are associated with better performance and lower HRV and an idling of beta/gamma power in both frontal and parietal areas. Instances of low attention lead to increased errors and increase in HRV concomitant with an increase in beta/gamma power in frontal and parietal cortices. TMS to the left frontal cortex disrupts these normal relationships, increases HRV in general and alters the normal brain response during task demands. Thus, it may be that TMS to the left frontal cortex alters synaptic dynamics that also affects the autonomic system to produce less of a cognitive reaction to instances of both high and low performance.

Disclosures: V. Razdan: None. **W. Legon:** None. **W.J. Tyler:** None.

Poster

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Topic: F.01. Human Cognition and Behavior

Support: CIHR MOP-119428

Title: Isolating regions involved in conflict monitoring and cognitive control: A multi-modal approach to reducing variability in regions of interest

Authors: *S. A. HOLMES[1], M. PETRIDES[1,2], L. M. KOSKI[1,2];
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Abstract: Background: Adaptation to brain injury involves a transition in how information is processed in the brain. As emerging pathways over-ride existing ones, conflicts in co-activation may be resolved through cognitive control. The accurate localization of frontal brain regions underlying conflict monitoring and cognitive control is critical to understanding such functional adaptation. Unfortunately frontal cortical regions host diverse neuronal populations and structural connectivity, making global definitions unsuitable for structural and functional analysis. Objective: To identify the anatomic and stereotaxic location of regions within the anterior cingulate cortex (ACC) and non-cingulate frontal cortex (NFC) involved in conflict monitoring and cognitive control, as indexed by the Stroop interference task. Method: We performed a review of functional neuroimaging studies using a Stroop interference task in the following databases: PubMed, Brainspell and BrainMap. Exclusion criteria included: clinical populations, population <18 years of age, and studies in non-human subjects. All coordinates reported within the NFC and ACC were extracted and converted to a common (MNI) space. Coordinates in the ACC and NFC were divided into left and right hemispheres and cluster analyzed with an indicator coordinate (IC) reflecting an a priori postulate concerning the approximate locations of our regions of interest (see Cieslik et al., 2013, Cerebral Cortex 23:2677). Target clusters containing our IC were extracted, anatomically validated with respect to morphological landmarks and wrapped using a convex hull. Results: Four hundred and twenty nine articles were identified of which 29 were retained for coordinate extraction. One hundred and two independent coordinates were isolated in the NFC and 27 in the ACC. Cluster analysis identified five clusters in the left NFC, seven in the right NFC, and three in each of the left and right ACC. Target clusters in the NFC were located in the intermediate frontal sulcus (left hemisphere - vertical segment; right hemisphere - horizontal segment); whereas target clusters in the ACC were located in the paracingulate sulcus (left) and the cingulate sulcus (right).

Conclusions: Accurate interpretation of functional network activity is contingent on accurate description of an ROI's location relative to anatomic landmarks as well as stereotaxic coordinates. We have demonstrated a novel method for isolating functionally relevant ROIs. This technique is useful when confronted with a large degree of variability in the location and anatomic labeling of regions identified in the functional neuroimaging literature.

Disclosures: **S.A. Holmes:** None. **M. Petrides:** None. **L.M. Koski:** None.

Poster

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Topic: F.01. Human Cognition and Behavior

Support: Academy of Finland grant #260054

Title: Dissimilar spatiotemporal activation patterns for multiple attention tasks revealed by representational similarity analysis of EEG and fMRI data

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Abstract: We conducted identical experiments with electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI) in order to examine the spatiotemporal dissimilarities in neuronal representations associated with auditory-visual attention and distractor stimuli. Our event-related experimental setup consisted of 1-back visual and auditory discrimination tasks. Orientation discrimination of a sinewave grating and pitch discrimination of sinewave tone were performed by healthy adult participants separately (selective attention), with or without concurrent stimuli in the non-attended modality, or simultaneously in both modalities (divided attention). Task difficulty and stimulus discriminability in each modality was kept at 70% threshold using an adaptive staircase method. Stimulus detection served as a control task. On 1/3 of trials, additional novel distractors, spectrally complex sounds and textures, coincided with the target stimuli. In total, there were 28 trial types corresponding to combinations of the attended modality, distractor modality, and attention task. The dissimilarities across trial types were analyzed with multivariate representational similarity analysis (RSA). Behavioral results showed that thresholds increased to two-fold in the divided-attention condition in comparison to

selective-attention condition. The distractors increased reaction times and decreased the amount of correct responses. Distractors within the attended modality interfered task performance more that distractors in the non-attended modality. Representational dissimilarity matrices (RDMs) across trial types were calculated and compared with model RDMs based on the experimental manipulations. Temporal RDMs were calculated from event related potentials (ERPs) occurring in EEG using consecutive 10-ms time windows. Significant peaks of correlation between measured and model RDMs were found at several time periods after stimulus onset, depending on the model: stimulus modality (140 ms), novelty processing (270 ms), and attention tasks (370, 430, and 520 ms). For fMRI data, a 3D searchlight (radius 3 voxels) method was used to find voxel clusters in which the activity patterns correlated with model RDMs. Stimulus-modality- and novelty-related voxel clusters were found in auditory and visual cortices and in parietal areas. Several attention-task-related voxel clusters were found in the dorsolateral prefrontal cortex. The results show separable temporal and spatial activity profiles for different trial types and suggest that attention modulates activity patterns in attention networks depending on the cognitive task.

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Poster

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Topic: F.01. Human Cognition and Behavior

Support: ARC DP120103721

Title: Distinct frontoparietal contributions to goal maintenance and goal directed orienting in visual search

Authors: ***J. M. G. VROMEN**[1], S. I. BECKER[1], R. W. REMINGTON[1], J. B. MATTINGLEY[2,1];
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Abstract: Human visual attention is subserved by a distributed frontoparietal brain network. The contributions of different cortical regions within this network to feature-driven attentional control remain to be clarified. We investigated which frontoparietal regions are associated with goal maintenance and goal directed orienting. We had 18 participants perform a visual search task while undergoing functional magnetic resonance imaging (fMRI). The visual search

displays were identical across conditions. Instructions were varied across blocks to independently manipulate the difficulty of goal maintenance (single- versus double-component target-set) and goal directed orienting (pop-out versus conjunction target search). As a first analysis step, an independent functional localizer was used to identify regions of interest (ROIs) that were active during goal maintenance and goal directed orienting. These ROIs were located mainly within a frontoparietal network, and included frontal cortex (bilateral cingulate gyri, middle frontal gyri, and right medial frontal gyrus) and parietal regions (bilateral superior parietal lobules and insula). Next we examined activity within the ROIs as a function of the level of difficulty of goal maintenance and goal directed orienting. Increased demands on goal maintenance were associated with greater activity within anterior frontal regions, including the left anterior middle frontal gyrus, bilateral middle frontal gyri, and the right insula. By contrast, increasing the difficulty of goal directed orienting was associated with larger increases in activity within more posterior frontal and parietal regions, including the left cingulate gyrus and the right superior parietal lobule. Our findings suggest that different cortical regions within the fronto-parietal attention network make distinct contributions to goal directed orienting and goal maintenance during visual search. These findings have important implications for understanding attentional deficits that arise after focal lesions (e.g., due to stroke), and for approaches to the management and treatment of such disorders.

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Poster

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Support: NIMH 092345 and James S McDonnell Foundation

Title: Dissociable effects of attention and expectation during orientation discrimination

Authors: *N. RUNGRATSAMEETAWEEMANA, S. ITTHIPURIPAT, J. SERENCES; UCSD, La Jolla, CA

Abstract: Top-down factors such as attention and expectation have been shown to modulate visual discrimination by improving the quality of sensory processing. However, few studies have examined these factors within the same experiment to determine if they operate via similar or

independent mechanisms (e.g., Kok et al., 2012). A previous psychophysical study has shown that the effects of attention and expectation on behavioral performance during orientation discrimination are dissociable depending on the amount of relevant sensory information available in the display. One possible explanation that could account for this finding is that attention and expectation may affect sensory evidence accumulation differently. To test this hypothesis, we presented subjects with a display containing moving dots, half of which were blue and half of which were red. On each trial, some percentage of the dots was rendered to move in the same direction. We manipulated attention (behavioral relevance) by cueing subjects to monitor either the red or blue lines (focused attention) or to monitor both (divided attention). Expectation of the target-defining motion direction was also manipulated by varying the ratio between target directions presented in a given block of trials. Finally, we examined interactions between the strength of sensory evidence and attention/expectation by manipulating the fraction of dots moving in the same direction on the target display across two levels (low and high coherence). Subjects were instructed to indicate their response using a flight-simulator joystick, while EEG data were recorded. Past studies suggested that the rate of the central parietal positivity (CPP) build-up during stimulus viewing is a neural correlate of sensory evidence accumulation (Kelly & O'Connell, 2013). We evaluated the effects of focused attention, expectation, and motion coherence, on the CPP to dissociate the impact of each factor on the rate of sensory evidence accumulation.

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Poster

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Support: National Research Foundation of Korea Grant (NRF-2013R1A1A2009029)

Title: Granger causal connectivity associated with attention network test

Authors: ***H. CHO**, M. KWON, J. CHOI, S. JUN;
Sch. of Information and Communications, Gwangju Inst. of Sci. and Technol. (GIST), Gwangju, Korea, Republic of

Abstract: The Attention network test (ANT) is an experimental paradigm to provide an assessment of alerting, orienting, and executive network via specific reaction time (RT).

Functional magnetic resonance imaging results have shown the anatomy of attentional networks. Studies of event-related potentials (ERP) associated with ANT also showed increased posterior N1 (alerting and orienting) and modulated P3 (executive). At present, it is unclear how the brain regions are communicate each other on different attentional states. Here, we show, with Granger causal connectivity (GCC) analysis, causal flow of three different attention networks can be measured by Electroencephalogram (EEG). Thirty-two healthy participants conducted ANT experiment. We calculate the ERP for cues and targets and then the MATLAB toolbox for GCC analysis was applied. For behavioral results, averages of alerting, orienting, and executive effect are 0.0356, 0.0744, and 0.0827 sec and the effects were significant ($p < 0.01$). We observed bigger cue-locked target N1 from alerting at Pz channel and modulated P3 at Fz as figure 1(A). Furthermore, the significant ($p < 0.01$ with Bonferroni correction) GCCs were plotted as figure 1(B). As previous studies reported that right frontal and parietal areas are active during the alert state, the activation of P3 causes Fz, F3, and F4 amplitude for center cue. The pulvinar, superior colliculus, superior parietal lobe, and frontal eye fields are often activated during the orienting state. For spatial cue, Pz amplitude causes central and posterior channels and Cz cause C3. As the anterior cingulate gyrus is an important part of the executive network, GCC in our results after incongruent target shows strong frontal connectivity compare to the congruent. In summary, we succeed to show ERPs and causal flows for three attentional networks and hope these measures can be applied to diagnosis patients with attention deficit

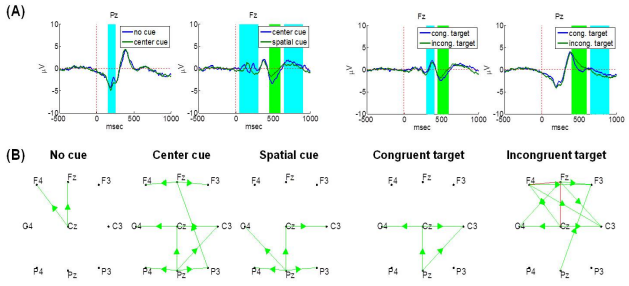

Figure 1. (A) Cue-locked target ERP. (B) First to fifth GCC plots are calculated from 0 to 2 sec after the no cue, center cue, spatial cue, congruent target cue, and incongruent target cue. Green and red lines mean unidirectional and bidirectional connectivity.

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Poster

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Title: Investigating brain connectivity with simultaneous TMS-fMRI

Authors: *D. RAHNEV, J. RIDDLE, D. SHELTRAW, B. INGLIS, M. D'ESPOSITO;
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Abstract: Characterizing the temporal and spatial pattern of brain connectivity is one of the critical challenges in cognitive neuroscience. Most current approaches take a correlational approach and are highly susceptible to artifactual findings stemming from confounds such as motion. This highlights the need for causal approaches in which a signal induced in one brain region can be observed to influence remote regions independent of subject motion. Simultaneous TMS-fMRI provides exactly such an approach. Nevertheless, its use has been limited due to (1) technical challenges and (2) insufficient knowledge of the effects of parameters such as stimulation intensity and number of pulses. To address some of the technical challenges in simultaneous TMS-fMRI, we developed a method to ensure microsecond level precision in the delivery of TMS pulses. This was done through a dedicated microntroller, which received TTL pulses from the scanner. The precision allowed us to employ a conventional EPI sequence without introducing temporal gaps for the TMS stimulation, as done previously. Instead, we targeted the crusher gradients, which come before and after the fat saturation pulse and last approximately 3.5 ms. Data from a phantom and human subjects demonstrated that TMS delivered in this way does not cause any artifacts in the BOLD signal. Next, we performed a series of experiments to characterize the influence of stimulation intensity and number of pulses on activity both under the coil and in remote regions. For each subject, we identified the location of the frontal eye fields (FEF) and middle frontal gyrus (MFG) based on their anatomical scans collected in a previous session. In different experiments we delivered 1, 2, 5, or 10 pulses at intensities between 50 and 120% of the subject-specific resting motor threshold (rMT). Stimulation was delivered at 11 Hz. We found that both higher intensity and higher number of pulses produced a monotonic increase in BOLD activations under the coil and in remote regions. We discuss the potential neural differences between equivalent BOLD activations produced by higher number of pulses delivered at lower stimulation intensity. The technical improvements and the characterization of BOLD response as a function of stimulation intensity and number of TMS pulses paves the way for introducing simultaneous TMS-fMRI as a mainstream technique in the toolbox of cognitive neuroscientists, and provide experimental support for its ability to characterize the pattern of brain connectivity.

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Poster

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Title: Source-localized EEG phase neurofeedback and its impact on brain activity - an exploratory simultaneous EEG-fMRI study

Authors: *B.-S. RAUCHMANN[1], D. KEESER[1,2], V. KIRSCH[3], B. STAMM[1], P. REIDLER[1], T. KARALI[1], R. THATCHER[4], S. KARCH[2], O. POGARELL[2], B. ERTL-WAGNER[1];
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Abstract: In previous studies it was shown that EEG neurofeedback (NFB) can be used to modulate brain activity. The aim of this study was to determine whether healthy subjects are able to modulate their neural activity using source-localized EEG phase NFB training. FMRI and EEG functional connectivity networks as well as task-based fMRI and EEG (Go- NoGo paradigm) were used to evaluate possible changes for real EEG-phase NFB compared to sham EEG-phase NFB. 27 healthy male subjects (19-30 years) underwent a 30 min. single session of LORETA based EEG-phase NFB (8 rounds à 3 min., 1 min. breaks between the sessions) in a sham-controlled experimental cross-over design. The NFB-protocol was based on bilateral hemispheric phase-synchronization of the alpha1, alpha2 and beta1-band (8-15 Hz) in the Brodman Area's (BA's) 7, 8, 9, 40 and 39. If subjects were able to increase EEG-phase synchronization for at least 1 sec. a visual feedback reward was given. Simultaneous EEG-fMRI recordings were done prior and post to real and sham EEG phase NFB followed by a Go- NoGo task. EEG recordings and Go- NoGo ERPs were also recorded outside the 3T MRI scanner. The preliminary results of the fcMRI measurements indicate that there is an up-regulation in the BA's 21 and 47 for the frontal-parietal network (FPN) and the default mode network (DMN) and a down-regulation in the BA's 45, 46, 9, 38, 20, 21, 22, 23 for the auditory network and the dorsal attention network (DAT) after real NFB compared to sham NFB. There were bigger clusters of reduced connectivity patterns (320 voxels) compared to increased functional connectivity clusters (79 voxels). The preliminary resting-state EEG results showed a global reduction in absolute power of the delta-band and the high-beta-bands and increased alpha-band EEG activity after real vs. sham NFB. For the ERPs we did not find a significant difference between real vs.

sham NFB. However, we found a reduced amplitude at Fz for the N2 component for the Go condition and an increased latency. The reaction time decreased for the Go trials for real NFB vs. baseline whereas there was no significant effect for the sham condition. The results also suggest that increased EEG alpha activity is negatively associated with the BOLD-signal in frontal-temporal brain regions. Furthermore, increased EEG alpha phase was associated with reduced delta- and theta-EEG power. Based on our results we conclude that EEG-phase neurofeedback may change brain activity in the short term. Behavioral and neurophysiological alternations support this conclusion. The changes in EEG and fMRI networks are widespread and should be confirmed in further studies.

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Poster

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Support: NIHR Grant WMCR NG0355

Wellcome Trust 49257

Title: The effect of transcutaneous direct current stimulation (TDCS) on brain connectivity and vigilance

Authors: *L. M. LI[1], R. BRAGA[2], C. DENTON[2], G. SCOTT[2], P. HELLYER[2], R. LEECH[2], D. J. SHARP[2];
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Abstract: Background: Non-invasive brain stimulation such as transcranial direct current stimulation (tDCS) can modulate brain function. Weak electrical currents are applied to the brain via scalp electrodes, resulting in transient changes in neuronal excitability. The mechanism by which tDCS might influence cognitive function is unclear, but functional MRI (fMRI) can be used to investigate its effects on brain network function. Our previous work has suggested that the functional connectivity of the right inferior frontal cortex (rIFC) is particularly important for cognitive control (e.g. Bonnelle et al PNAS 2012; 109(12): 4690-95), with increased

connectivity associated with greater attention. Therefore, we aimed to investigate the effect of tDCS on rIFC functional connectivity and attention. Methods: We conducted a single-blinded, cross-over, sham-controlled tDCS-fMRI study. Healthy right-handed subjects (n=12) underwent 2 sessions of 20mins of rIFG tDCS stimulation (sham or anodal). Sessions were separated by 60minutes and the order was randomised. The anode was placed over F8 and the cathode over the left shoulder. During each session, subjects performed the Choice Reaction Task (CRT) to assess processing speed and sustained attention. Subjects had resting state fMRI before and after each stimulation session. Functional connectivity was analysed using a dual regression approach in FSL. Results: Anodal tDCS to the rIFC increased functional connectivity between the stimulated area and superior parietal parts of the dorsal attention network (DAN) compared to baseline. Compared to sham stimulation, anodal tDCS produced effects of borderline significance on functional connectivity, with increased connectivity to areas involved in cognitive control network, including lateral occipital and temporoccipital areas. Compared to baseline, sham stimulation produced no significant changes in functional connectivity. Anodal tDCS improved vigilance level towards the end of CRT performance, when sustained attention typically falls. However, this effect was also seen with sham stimulation. Conclusion: Our results suggest that anodal tDCS of the rIFG can modulate connectivity within a network of regions involved in cognitive control, with the strongest effects seen as increased connectivity to the dorsal attentional network.

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Topic: F.01. Human Cognition and Behavior

Support: Wellcome Trust

Title: Phase dependent modulation of cortical activity produced by transcranial alternating current stimulation

Authors: *I. R. VIOLANTE[1,2], L. M. LI[1], T. REED[1], D. W. CARMICHAEL[3], J. C. ROTHWELL[2], D. J. SHARP[1];
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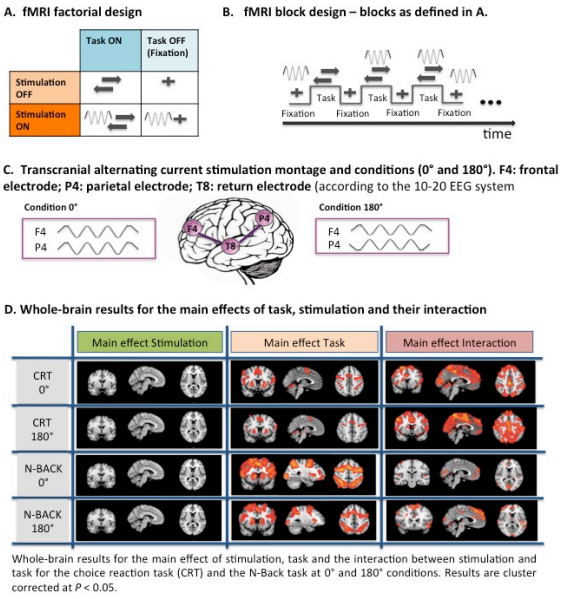
Abstract: Background: Transcranial brain stimulation is an increasingly popular tool used to influence brain function and cognition. However, its mechanism of action is usually unclear. Although technically challenging, combining stimulation with functional (f) MRI allows direct measurement of its effect on neural activity. Here, we report a pioneering study combining intermittent transcranial alternating current stimulation (tACS) and fMRI. A factorial design (Figure A) allowed us to test the hypothesis that the influence of tACS on brain activity depends on cognitive task performance and the phase of stimulation. Methods: Concurrent tACS and fMRI was acquired in a single-blinded, cross-over study on 20 healthy participants. TACS was targeted to regions involved in cognitive control and delivered over the prefrontal and parietal cortices at 6 Hz in two conditions: "synchronized" (0° phase difference) or "desynchronized" (180° phase difference) (Figure C). Participants performed the Choice Reaction (CRT) and the N-back Tasks. Stimulation was delivered in a counterbalanced and pseudorandom fashion during task (30 s) and rest (20 s) (Figure B). Standard FSL analysis of fMRI using ANOVA GLM was used. Results: TACS showed effects on brain activity that were dependent on cognitive task performance and stimulation phase (Figure D). Expected patterns of activity were observed for the CRT and N-back. A significant interaction between task and stimulation was present for both tasks, as the result of increased brain activity during stimulation. Moreover, phase dependent changes in cortical activity were observed in the direct comparison of 0° and 180° conditions. Participants were not able to distinguish blocks of stimulation from blocks of no stimulation. Importantly, fMRI images were not contaminated by tACS artefacts. Conclusion: We demonstrate that tACS modulates brain activity in a phase-dependent way that interacts with cognitive task performance. Combined TACS/fMRI acquisition is a powerful method to understand the mechanistic effects of brain stimulation.



Whole-brain results for the main effect of stimulation, task and the interaction between stimulation and task for the choice reaction task (CRT) and the N-Back task at 0° and 180° conditions. Results are cluster corrected at $P < 0.05$.

Disclosures: I.R. Violante: None. **L.M. Li:** None. **T. Reed:** None. **D.W. Carmichael:** None. **J.C. Rothwell:** None. **D.J. Sharp:** None.

Poster

818. Human Cognition and Behavior: Attentional Networks

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 818.14/BB3

Topic: F.01. Human Cognition and Behavior

Support: Wash U/NIH Grant UL1 TR000448

Wash U/NIH Grant TL1 TR000449

Title: Electroencephalographic correlates of lateralized spatial attention

Authors: *R. CHACKO[1], A. DAITCH[1], N. SZRAMA[1], M. CORBETTA[2], E. C. LEUTHARDT[2];
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Abstract: Humans can covertly deploy attention to locations they are not foveating on. This cognitive function is important for planning eye movements and is damaged in stroke patients with hemispatial neglect. Goal-directed shifts in spatial attention are governed by a pair asymmetrical, inter-hemispheric brain networks. The temporal dynamics of these networks are investigated in the present study with electrocorticography (ECoG), which has emerged as an investigative tool for understanding cortical dynamics. We hypothesize that parietal-occipital alpha and gamma power will best predict the locus of attention. The objective of this study is to characterize the spectro-spatial predictors of lateralized covert spatial attention in ECoG. Seven patients with intractable epilepsy were implanted with subdural ECoG grids. ECoG activity and behavioral responses were recorded while subjects performed a modified version of the Posner spatial cueing task. During each trial a central cue directed subjects to attend to a locations to the left or right of the cue. Subjects were required to identify the target, which appeared at the cued location 80% of the time. We use a Gabor wavelet filter bank for spectral decomposition. We cluster-based permutation test to identify spectro-spatial predictors of lateralized covert spatial attention. We found that spectral power changes in the alpha, beta and gamma bands over parietal, temporal and sensorimotor cortices are correlated to task demands. Network-mapped electrodes reveal opposing power dynamics across attentional networks.

Disclosures: R. Chacko: None. **A. Daitch:** None. **N. Szrama:** None. **M. Corbetta:** None. **E.C. Leuthardt:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurolutions.

Poster

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Topic: F.01. Human Cognition and Behavior

Support: NWO Research Talent 406-13-018

ERC FP7-SP2 [263472]

Title: Neural correlates of attentional benefits and costs: an fMRI study

Authors: *H. C. LÜCKMANN, F. DUECKER, V. VAN DE VEN, H. I. JACOBS, A. T. SACK;
Cognitive Neurosci., Maastricht Univ., Maastricht, Netherlands

Abstract: Covert shifts of attention to a cued location speed up detection and discrimination processes at that location (attentional benefits) and increase the time needed to react to stimuli at uncued locations (attentional costs). The magnitude of these attentional benefits and costs varies in healthy subjects and is altered in patients with attentional disorders such as spatial neglect. Studies of the neural network mechanisms underlying these interindividual differences considerably contribute to our understanding of spatial attention. Previous neuroimaging studies investigating spatial attention have often omitted a neutral cue condition, therefore not being able to differentiate benefits and costs. However, this is important, as the neural mechanisms underlying benefits and costs seem to be at least partially independent. Here, we investigated the relationship between functional mechanisms in large-scale neural networks and attentional benefits and costs on the individual level. We used an endogenous spatial cueing paradigm with central symbolic cues. Participants ($N = 15$) performed an orientation discrimination task. On each trial, either one (directive) or both (neutral) hemifields were cued, and directive cues predicted subsequent target location with 75% validity. We recorded and analysed cue effects on reaction times (RTs). Whole-brain functional MRI data of participants was acquired at a fieldstrength of 3T. We obtained participant-specific maps corresponding to well-known functional networks. These individual maps were fed into higher-level analyses to find network characteristics that show a relationship with individual attentional benefits and costs. Attentional benefits and costs were observed in all participants, with variable magnitude of the cue effects. We associated these interindividual differences with functional variations in the investigated networks. Results contribute towards a more complete account of the neural correlates of spatial attention. Considering that attention is one of the core cognitive mechanisms needed for

everyday functioning, and that it is frequently impaired in neuropsychiatric diseases, our findings are of particular interest for the development of neuromodulatory interventions targeting large-scale brain networks to boost cognition in health and disease.

Disclosures: H.C. Lückmann: None. **F. Duecker:** None. **V. van de Ven:** None. **H.I. Jacobs:** None. **A.T. Sack:** None.

Poster

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John Templeton Foundation Grant 39970

Hershey Family

Tan Teo

Yoga Research and Education

Mental Insight

Baumann Foundations

Title: Longitudinal modulations of cortical responses during a visual continuous performance task: Effects of practice or intensive meditation training?

Authors: *C. E. POWERS[1], A. P. ZANESCO[2], K. R. WINEBERG[1], B. G. KING[2], K. A. MACLEAN[1], S. R. AICHELE[3], M. SAGGAR[4], D. A. BRIDWELL[5], T. L. JACOBS[1], A. WALLACE[6], C. D. SARON[1];
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Abstract: Intensive meditation training that involves sustained selective attention on a target (e.g. breath) increases perceptual sensitivity and enhances vigilance to an extent that improves response behavior on a 32 minute continuous performance task (CPT) involving detection of

brief line length differences set to perceptual thresholds (Maclean et al, 2010). Here we aim to identify patterns of neural activity obtained during the CPT that are consistent with these behavioral data. We analyzed 88-channel event-related potentials (ERPs) recorded from 10 participants who performed the CPT six times: as a matched control group before, during, and after a 3-month meditation retreat training consisting of ~6 hours of meditation per day, and 3 months later as they underwent identical meditation training and completed the CPT before, during, and after their own 3-month retreat. Visual ERPs to unchanging non-targets (90% probability, ISI ~2 s) were expected to be modulated in response to training. This would reflect top-down control of perceptual sensitivity to non-target- (and target-) related visual information. Scalp topographic maps of current source density (CSD) obtained from the first CPT assessment of each subject as either control or trainee and were used to identify, on a per hemisphere/individual basis, the electrode closest to the current focus of the peak intensity of N1 ERP component. CSD waveforms from each hemisphere/individual/testing condition (control vs. trainee) were overlain and the N1 examined. Practice effects were observed in half the sample with considerable variability that showed patterns of both decreasing and increasing N1 negativity (current inflow) with task repetition. N1 onset or offset latency did not vary systematically with practice. In contrast, these same subjects, as trainees, showed a marked and consistent pattern (9 of 10 Ss for the right hemisphere) of N1 modulation by training of onset and/or offset latency. We interpret this training-related effect as due to efficient regulation of attentional resources and visual processing in support of task goals. These data will be discussed in relation to prestimulus alpha oscillatory patterns to investigate whether the training-related N1 changes are due to proactive up-regulation of attentional focus prior to stimulus presentation that begets increased perceptual sensitivity to targets to an extent that facilitates target detection. This work helps identify neurocognitive aspects of attention that are affected when attentional skills are cultivated with intensive meditation training and how such training may affect performance in other attention-demanding tasks.

Disclosures: **C.E. Powers:** None. **A.P. Zanesco:** None. **K.R. Wineberg:** None. **B.G. King:** None. **K.A. MacLean:** None. **S.R. Aichele:** None. **M. Saggar:** None. **D.A. Bridwell:** None. **T.L. Jacobs:** None. **A. Wallace:** None. **C.D. Saron:** None.

Poster

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Support: Fetzer Institute Grant 2191

John Templeton Foundation Grant 39970

Hershey Family

Tan Teo

Yoga Research and Education

Mental Insight

Baumann Foundations

Title: Resting EEG θ/β ratios increase reliably over the course of intensive three-month meditation retreats

Authors: A. C. SKWARA[1,2], B. G. KING[1,2], A. P. ZANESCO[1,2], C. E. POWERS[2], K. R. WINEBERG[2], M. SAGGAR[3], S. R. AICHELE[4], D. A. BRIDWELL[5], T. L. JACOBS[2], K. A. MACLEAN[2], B. K. SAHDRA[6], E. FERRER[1], B. A. WALLACE[7], *C. D. SARON[2];
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Abstract: Despite evidence that contemplative training is associated with improved attentional capacity and emotional well-being, the physiological bases of these trait changes remain unknown. To approach this question, we investigated changes in resting EEG activity across a 3-month residential meditation retreat (R1). Trainees (N=30) received instruction in shamatha meditation, aimed at cultivating attentional stability and beneficial aspirations for self and others. They practiced meditation ~6 hr/day and completed a battery of self-report and laboratory assessments pre-, mid-, and post-retreat. Matched wait-list controls (N=30) were flown to the retreat center for these same assessments and 3 months later underwent their own separate 3-month retreat (R2). Here we focus on EEG θ/β ratios in 2 min of eyes-open rest. θ/β has been implicated as a marker of attentional and affective traits. Increased θ/β is associated with disorders of attention and reduced emotion regulation capacity, and has been hypothesized as a marker of decreased cortical control of approach motivation (increased impulsivity). Mean CSD values (73-chan) were extracted for each subject and timepoint. Four 6-electrode clusters, left and right frontal (**F**) and parietal (**P**), were created. Cluster means were log-normalized and θ/β was calculated for each timepoint. Mixed effects models for **F** and **P** clusters with hemisphere as a factor tested longitudinal changes in θ/β across timepoint and group status (trainee, control). In R2, significant main effects were found for Timepoint in **F**, $F(2,237)=20.8, p<0.0001$, and **P**, $F(2,237)=16.99, p<0.0001$, and Status in **F**, $F(1,237)=48.5, p<0.0001$, and **P,** $F(1,237)=54.3, p<0.0001,$ clusters, as well as an interaction of Timepoint x Status in **F,** $F(2,237)=9.2$,

p=0.0001, and **P**, *F(2,237)=7.5, p=0.0007*. Mean **F** and **P** θ/β increased pre- to post-retreat in trainees, but not controls. All effects replicate in R1. Analyses comparing R1 to R2 *trainees only* revealed a main effect of Timepoint in **F** and **P** clusters, but no effect of Group or Group x Timepoint interaction, indicating consistency across retreats. Despite links between increased θ/β and difficulty with cognitive-affective regulation, previous analyses of these trainees have revealed improved response inhibition and decreased self-reported difficulty with emotion regulation following training. These findings suggest a potentially complex relation between cognitive-affective regulation and θ/β in intensive meditation training such that increased θ/β may not reflect regulation difficulty per se, but rather a greater trait-like capacity to engage with and flexibly attend to one's present-moment experience.

Disclosures: **A.C. Skwara:** None. **B.G. King:** None. **A.P. Zanesco:** None. **C.E. Powers:** None. **K.R. Wineberg:** None. **M. Saggar:** None. **S.R. Aichele:** None. **D.A. Bridwell:** None. **T.L. Jacobs:** None. **K.A. MacLean:** None. **B.K. Sahdra:** None. **E. Ferrer:** None. **B.A. Wallace:** None. **C.D. Saron:** None.

Poster

818. Human Cognition and Behavior: Attentional Networks

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Program#/Poster#: 818.18/BB7

Topic: F.01. Human Cognition and Behavior

Support: CELEST, an NSF Science of Learning Center (SBE-0354378)

Title: Attention-modulated neural responses to a dynamic visual selective attention task

Authors: ***S. BRESSLER**[1], L. BONACCI[2], J. A. KWASA[2], B. SHINN-CUNNINGHAM[1]; [1]CompNet, [2]BME, Boston Univ., Boston, MA

Abstract: Successful interaction with the outside world is guided by an individual's ability to selectively attend rapidly changing targets while ignoring interfering stimuli. In the auditory domain, our lab has shown that selective attention enhances the neural representation of attended sounds while simultaneously suppressing the representation of competing stimuli. While auditory attention studies require subjects to attend a target stream over time, visual attention studies, by comparison, typically require subjects to detect a single change to a static image at a prescribed spatial location. In this study, we asked whether the temporal dynamics of auditory selective attention could be observed in an analogous visual task. Two competing sequences of flashing arrows were presented to the left and right of a central fixation point (4.8 degrees

eccentricity). In each sequence, the arrow orientations varied, creating trajectories that were either rising, falling, or zig-zagging. A cue at the start of each trial instructed subjects either to covertly attend to the left sequence (1/3 of trials) or right (1/3 of trials) sequence and identify the shape of the corresponding arrow trajectory, or to withhold responses (passive control; 1/3 of trials). The onsets of the arrows in the two streams were staggered, allowing the event-related potentials (ERPs) evoked by each arrow to be isolated temporally. Scalp potentials were simultaneously recorded using a 64-channel EEG setup. The N1 amplitudes evoked by arrows in the attended stream were greater than those evoked by arrows in the ignored stream. This effect was greatest in right parietal-occipital scalp electrodes when the stimulus was presented in the left visual field, consistent with a contralateral representation of external space in occipital lobe. N1 responses in the passive control condition were smaller than in either attend condition. Changes in ERP strength were paralleled by changes in alpha oscillations (8-12 Hz), which were stronger in parietal-occipital sensors contralateral to the ignored stream. The observed top-down modulation of ERPs evoked by events in ongoing visual streams and the associated changes in alpha oscillations are similar to those previously observed in an analogous auditory task. Based on findings from a cross-modal fMRI study from Michalka et al. (under review), we suggest that stimuli rich in temporal features engage similar spatial attention networks in intraparietal sulcus. Understanding how visual and auditory attention operate can yield insight into the different brain networks engaged by attention.

Disclosures: **S. Bressler:** None. **L. Bonacci:** None. **J.A. Kwasa:** None. **B. Shinn-Cunningham:** None.

Poster

818. Human Cognition and Behavior: Attentional Networks

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Program#/Poster#: 818.19/BB8

Topic: F.01. Human Cognition and Behavior

Support: NIH RO1EY022229

NSF CELEST SMA0835976

NSF DGE1247312

Title: Auditory-biased and visual-biased attentional subdivisions in the cerebellum revealed by functional magnetic resonance imaging

Authors: *E. J. LEVIN[1], A. L. NOYCE[1], S. W. MICHALKA[1], J. A. BRISSENDEN[1], M. A. HALKO[2], D. C. SOMERS[1];
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Abstract: Increasing evidence from behavioral and neuroimaging studies implicates the cerebellum in higher-order cognitive processes. Our laboratory has recently observed that within the caudo-lateral frontal cortex there exist visual-biased and auditory-biased attention subdivisions within a greater multiple demand network (Michalka et al.). This includes two frontal regions biased for visual-attention, superior precentral sulcus (sPCS) and inferior precentral sulcus (iPCS), interdigitated with two regions biased for auditory-attention, transverse gyrus intersecting precentral sulcus (tgPCS) and caudal inferior frontal sulcus (cIFS). Ongoing work from our lab has also shown that visual working memory and sustained visual attention tasks recruit specific regions of the cerebellum. Prior work (Buckner et al., 2011) demonstrates that resting-state functional connectivity networks in the cortex also extend to include sub-networks within the cerebellum. We found that attentional recruitment is specific to cerebellar nodes that exhibit strong intrinsic functional connectivity with the cortical dorsal attention network. The present research investigates whether these 'cerebellar nodes of the dorsal attention network' possess sub-regions biased for auditory attention or visual attention, similar to our observations in lateral frontal cortex. We used fMRI to investigate whether cerebellar attention regions are biased for audition versus vision, or are unbiased (multiple demand). Subjects performed a 2-back task on auditory and on visual stimuli. The contrast of auditory 2-back vs. visual 2-back revealed interdigitated visual-biased and auditory-biased regions in lateral frontal cortex as well as sensory-biased regions in posterior cortex (see Noyce et al., this meeting). Additionally, we employed resting-state functional connectivity using the cortical visual-attention network and auditory-attention network to define regions of interest within the cerebellum. We observed segregated auditory-attention and visual-attention sub-regions within the posterior lobe of the cerebellum. Bilateral visual attention activation was observed relatively dorsal and medial to the bilateral auditory attention activation within the cerebellar vermis. More dorsal regions of the cerebellar vermis exhibited stronger multiple demand characteristics. Our results indicate that a pair of sensory-biased attention networks recently observed in cortex extends to include regions of posterior cerebellum. More broadly, our results contribute to a growing body of evidence demonstrating cerebellar contributions to higher-order cognition.

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Poster

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R01NS078396

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Title: Auditory attention modulates frontal and temporal oscillatory dynamics in humans: Evidence from electrocorticography

Authors: *R. VAN DER MEIJ[1], A. BIDET-CAULET[2,3,4], J. PARVIZI[5], N. CRONE[6], E. CHANG[7], R. T. KNIGHT[3,4], B. VOYTEK[1];
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Abstract: The brain needs to flexibly route information in distributed neuronal networks to meet the needs of rapid environmental changes. This selective communication between neuronal populations could be achieved via oscillatory dynamics. One such oscillatory phenomenon is phase-amplitude coupling (PAC), which reflects the hierarchical modulation of oscillations at different frequencies, but also the phase-coupled modulation of local neuronal spiking activity. The latter, manifested as high gamma activity (HG; 70-250 Hz) is modulated by oscillations at multiple frequencies dependent on task demands. HG can be observed as broadband increased power in the power spectrum of micro- to mesoscale measurements in human electrocorticographic data obtained from subdural recordings (ECoG). Recent evidence suggests that the power spectrum, which reflects both oscillatory and non-oscillatory processes, can provide insight into the dynamics supporting goal-directed behavior. Notably, an upward rotation (flattening) of the power spectrum could reflect a shift in neuronal resources from a regime of tight oscillatory inhibition towards one of increased sensitivity to incoming signals. Local HG activity has been shown to be modulated by low frequency rhythms that are coherent over broader regions suggesting that power spectral changes could be coordinated in a similar manner. To investigate this, we obtained ECoG recordings from 8 epilepsy patients undergoing resective

surgery while they performed a dichotic attention task. They had to detect deviant sounds within a relevant stream while ignoring an irrelevant acoustic stream. A third condition (control condition) was added in which all sounds received the same amount of attention. We found that fronto-temporal HG activity increased, frontal theta increased, and temporal alpha decreased as a function of attention. Additionally, we also observed upward rotations (a flattening) of the power spectrum at temporal electrodes, which captures both the decrease of temporal alpha, and the increase of temporal HG activity. Moreover, this spectral flattening was found to be phase-locked to distributed frontal theta rhythms, suggesting temporally coordinated changes in neuronal recruitment. Taken together, these results show the modulation of local neuronal activity by distributed oscillatory rhythms as a function of task demands. Importantly, this modulation occurred (1) on timescales as short as several 100ms, and (2) between distinct regions including auditory cortex and frontal areas. The results provide evidence that oscillatory dynamics provide a key mechanism for routing of information in the brain.

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Poster

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Topic: F.01. Human Cognition and Behavior

Support: Hersenstichting Nederland Grant 2013(1)-245

Title: Act based on what you expect: Cue-induced expectancy modulates alpha and theta oscillations

Authors: K. A. BANGEL[1], H. A. SLAGTER[2], *D. DENYS[1], A. MAZAHERI[1,3];
[1]Academic Med. Ctr. Univ. of Amsterdam, Amsterdam, Netherlands; [2]Dept. of Psychology, Univ. of Amsterdam, Amsterdam, Netherlands; [3]Sch. of Psychology, Univ. of Birmingham, Birmingham, United Kingdom

Abstract: We are constantly guided by our expectations about upcoming events, which significantly influence what our attention is focused on. A number of previous studies have examined how expectation modulates the neural responses to an expected event. In contrast, the objective of this study was to explore how expectation influenced neural processes related to preparation. We investigated how expectancy about task difficulty in a visual search task

modulated oscillatory activity in the EEG, and the consequence of this modulation on the filtering of task-irrelevant information. Specifically, we examined how expectation about task difficulty modulated oscillatory activity in the theta (3-5 & 5-7 Hz), alpha (8-12 & 12-16 Hz), and beta band (16-20 Hz) prior to the onset of the visual search array. A number of previous findings have shown that the disengagement of a sensory system not important for a given task is achieved by an increase in oscillatory alpha and beta activity. In contrast an increase in theta activity has been linked to higher cognitive executive functions such as cognitive control. EEG was recorded from 14 participants who performed a visual letter search task under varying task demands. Audiovisual low and high load cues were used to generate expectancy about the likely load of the upcoming visual search task (i.e. task difficulty; Sy et al, 2014). We found a transient increase in alpha (~200-300 ms) and beta power (~370-410 ms) over sensorimotor areas following high load cue onset in the pre-stimulus interval. A transcient increase in theta power over occipital regions (660-990 ms) followed. Validly cued high load targets induced a transient increase in midline theta power about 960 ms after stimulus onset. Post-stimulus theta power positively correlated with task performance measured in reaction times on a trial-by-trial basis. We speculate that the increase in alpha power induced by high load cues indexes preparatory blocking of task-irrelevant processes as a way to allocate cognitive resources to the more difficult task. The increase in theta power with high load cues, and its positive correlation with reaction times could be related to higher response monitoring and more careful response strategies. These results together suggest that expectancy created by cue evaluation may adjust the brain for the upcoming task by inhibiting task-irrelevant processing and engaging online control processes. References Sy, J. L., Guerin, S. A., Stegman, A., & Giesbrecht, B. (2014). Accurate expectancies diminish perceptual distraction during visual search. *Fr. in human neurosc*, 8, 344.

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Poster

818. Human Cognition and Behavior: Attentional Networks

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Topic: F.01. Human Cognition and Behavior

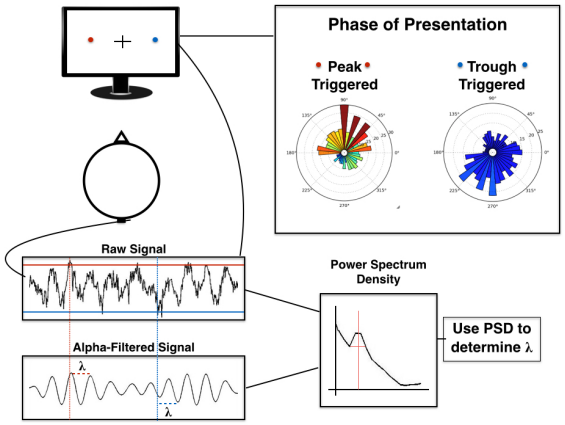
Support: Alfred P. Sloan Foundation Research Fellowship

UC San Diego Qualcomm Institute Calit2 Strategic Research Opportunities Program

Title: Influencing visual target detection with oscillatory phase-specific stimulus presentation

Authors: *R. J. GOUGELET[1], T. DONOGHUE[1], M. PIPER[2], A. ALTHOFF[3], T. P. URBACH[1], B. VOYTEK[1];
[1]Dept. of Cognitive Sci., [2]Dept. of Philosophy, [3]Dept. of Computer Sci. and Engin., UCSD, La Jolla, CA

Abstract: We investigated the extent to which ongoing electroencephalography (EEG) neural oscillations emanating from fronto-parietal and occipital scalp regions in the theta (3-7 Hz) and alpha (8-12 Hz) frequency ranges contribute to the detection of visual stimuli in humans. We first observed how subject-specific alpha phase affects the detection of a cued, near-threshold visual target such that the visual cortical alpha phase at the time of visual stimulus onset biased target detection, replicating previous reports. We extended these observations by presenting visual targets at specific phases of the ongoing oscillatory alpha using a real-time oscillatory phase tracking system. We implemented online phase tracking in two ways, and compare the efficacy of them both. In the first, we sampled the ongoing EEG datastream and peak filtered it using a phase- and group-delay compensated Parks-McLelland FIR digital bandpass filter, centered at the predetermined maximum amplitude and center frequency of the subject-specific ongoing alpha oscillation. Periods when the ratio of alpha/broadband power reached a predetermined threshold were isolated for phase detection. Peaks and troughs of the filtered datastream were then extracted to determine the periodic timing of the ongoing alpha phase. We extrapolated the timing characteristics of the detected peaks to predict peak and trough phase intervals beyond the causal window of the datastream, and presented stimuli during such intervals in real-time. In the second, we recorded a few minutes of resting EEG to identify individual visual cortical alpha center frequency. These data also allow us to identify alpha peaks and troughs using a simple thresholding procedure wherein the top and bottom 0.1% of the sorted amplitude values of the raw, ongoing EEG reflect, with high accuracy, individual alpha peaks and troughs. Given the stability of the alpha occipital rhythm over short time frames, we attempted to present stimuli during specific phases of the dominant oscillatory alpha using this method as well.



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Poster

818. Human Cognition and Behavior: Attentional Networks

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Topic: F.01. Human Cognition and Behavior

Support: Alfred P. Sloan Foundation Research Fellowship

UC San Diego Qualcomm Institute Calit2 Strategic Research Opportunities program

Title: Oscillatory visual cortical alpha disruptions in age-related working memory impairments

Authors: ***T. TRAN**[1], N. HOFFNER[2], B. VOYTEK[3];
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Abstract: Neural oscillations in the visual cortex play an important role in attention and memory. Oscillations, in particular 8-12 Hz alpha activity, support interregional communication, and ongoing fluctuations in alpha power and phase bias perception and cognition. While these phenomena are fairly well characterized individually, here we examine the overlap between visual attention and working memory and how these oscillatory processes are affected by healthy aging. We used electroencephalographic (EEG) recordings to compare behavioral performance and alpha activity of younger and older adults (20-30 and 60-70 years old) during a lateralized, visual working memory task. In this task, subjects were first presented with a non-informative, foveally-presented alerting cue indicating the beginning of a trial. This cue was followed by brief presentation of a visual working memory array and a delay period. Subjects then reported if a second, test array was the same as or different from the memory array. In this task, older adults showed increased reaction times overall and decreased accuracy in high memory load trials. Both groups showed decreased contralateral delay activity with increasing memory load. Analysis of extrastriate alpha power revealed decreased contralateral power during the delay period in both groups. While older adults also showed decreased ipsilateral alpha power, younger adults showed increased ipsilateral power instead, revealing significant lateralized alpha power differences as a function of age. Analysis of alpha phase revealed that, while memory array presentation equally increased extrastriate phase-resetting (or intertrial coherence, ITC) in both groups, younger adults showed strong alerting-cue-induced ITC that was nearly absent in older adults. These results suggest that in performing this task, older adults make less use of the

alerting cue than do younger adults, and older adults may rely more heavily on bilateral visual cortical attention systems than do younger adults.

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Poster

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Topic: F.01. Human Cognition and Behavior

Support: R01 NS055829

5T32NS00722429

5T32GM00720538

Title: Intracranial EEG signatures of conscious visual experience

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[1]Neurol., [2]Neurosurg., [3]Neursurgery, [4]Neurobio., Yale Univ., New Haven, CT

Abstract: Recent advances in brain imaging have begun to show the whole-brain anatomy of areas involved in forming a conscious experience of visual awareness that results in subsequent report. Direct human electrophysiology techniques can also be used to uncover the temporal progression of neural activity throughout the brain during these events. We have developed a visual threshold perception task that elicits brief conscious events using a target face stimulus with contrast calibrated to a 50% detection rate. These events are validated by subsequent report of perception and location. The Yale Epilepsy Surgery Program implants some 100-300 subdural intracranial electrodes sampled at 1024 Hz in patients undergoing observation for intractable epilepsy. Eight such patients were recruited to perform our behavioral task during their inpatient stay. Stimulus perception rate was 55% (±3% SEM) when the target was present whereas false positive rate was 18% (±6% SEM) for blank trials. In true positive perception trials, subjects could correctly indicate the location of the stimulus in 1 of 4 quadrants 87% (±3% SEM) of the time. In true negative perception trials, the location accuracy was only 28% (±3%), close to chance levels. These behavioral results demonstrate appropriate subject engagement and performance in the task. Analysis of electrocorticography (ECoG) results show that perceived

and correctly located ("confirmed perceived") trials compared to not perceived and incorrectly located ("confirmed not perceived") trials have largely divergent event-related potentials (ERPs) in higher visual processing areas as well as fronto-parietal cognitive and medial temporal memory networks as early as 200 ms and beyond 1000 ms post-stimulus despite same contrast level. However, the early (<200 ms) ERPs in electrode contacts located directly in primary visual cortex show identical waveforms between confirmed perceived and confirmed not perceived trials. The late latency ERPs are sometimes also accompanied by high-frequency (65-115 Hz) power changes, suggesting higher-order cognitive processing in neurons at those locations. Lower frequency alpha and theta-range oscillations are found to be phase-locked to stimulus onset for confirmed perceived trials and phase-shifted for confirmed not perceived trials. These findings suggest that state-related fluctuations in the brain may gate the access of primary visual sensory information to higher cortical circuits necessary to form a conscious experience. Additional analyses of the temporal sequence of these signals may uncover network-related changes that are responsible for producing brief conscious events.

Disclosures: **W.R. Xiao:** None. **R.E. Smith:** None. **G.J. Touloumes:** None. **C.L. Horien:** None. **A. Raja:** None. **E.C. Morse:** None. **R.E. Watsky:** None. **S.A. Weiss:** None. **S.A. Weiss:** None. **W.C. Chen:** None. **D.D. Spencer:** None. **J.L. Gerrard:** None. **H. Blumenfeld:** None.

Poster

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Topic: F.01. Human Cognition and Behavior

Support: the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (No. 2014R1A2A2A04003858)

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Title: Alteration of inhibition of return in involuntary visuospatial attention in the patients with rapid-eye movement sleep behavior disorder

Authors: ***M. JEONG**[1], K. CHA[1], J. CHOI[1], J.-S. KYONG[2], B. LEE[2], B.-W. LYU[2], D. JUNG[2], S. KU[2], T.-J. KIM[2], J.-S. SUNWOO[2], J.-I. BYUN[2], K.-Y. JUNG[2], K. KIM[1];
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Abstract: Rapid eye movement (REM) sleep behavior disorder (RBD) is a sleep disorder characterized by dream enactment behavior and the loss of muscle atonia during REM sleep. Recent neuropsychological tests reported abnormality in visuospatial attention in the patients with RBD. However, neurophysiological evidence about the abnormality has not been reported yet. In this study, we investigated cortical activities associated with abnormal visuospatial attention in RBD patients, focusing on neural synchronies in theta-band rhythms. Drug-naïve idiopathic RBD patients and healthy controls were involved in this study. Subjects performed Posner's cueing paradigm in which they were asked to discriminate targets (red or yellow asterisk, with 50:50 probability) and to respond by button press. The targets were presented in two boxes located at each side of central fixation. Before targets were presented, border of the box was highlighted so that subjects could covertly turn their attention to the box (cue). The time intervals between cue and target (stimulus onset asynchrony, SOA) were 200ms and 1000ms with 50:50 probability. Sixty channel electroencephalograms (EEGs) were recorded during the task. In addition to target-elicited event-related potential (ERP) analysis, evoked theta-band activity (TBA) and theta-band phase synchronization (TBPS) were analyzed to investigate local- and long-range neural synchronies. Significant TBPS patterns were analyzed using weighted graph theoretical measures, including the degree (*K*), clustering coefficient (*C*) and global efficiency (*E*). For short SOA task, the reaction time (RT) was reduced for valid condition compared to invalid condition, in both control and RBD groups (cuing effect). To the contrary for long SOA task, the RT was delayed for valid condition (inhibition of return, IOR effect). In both control and RBD groups, behavior cueing effect for short SOA was accompanied with an increase of P1 ERP component, strong TBA and TBPS, as well as more efficient theta-band network for valid condition. On the other hand, behavior IOR effect for long SOA was associated with a decrease of N1 ERP component, weak TBA and TBPS and less efficient theta-band network for valid condition. The phenomenon for long SOA was shown only in control. We found that several neural activities reflected the well-known cueing and IOR effects during visuospatial attention tasks in healthy controls. The measures reflecting cueing effect were varied in the same manner in RBD patients as in controls. However, the measures reflecting IOR effect was found only in controls. This may imply the dysfunction of attentional inhibitory system in RBD patients.

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Poster

819. Human Cognition: Attentional Networks

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Support: European Research Executive Agency grant PCIC10-GA-2011-304201 (FP7-PEOPLE-2011-CIG)

Title: The impact of unexpected salient sounds: increase in arousal versus attentional capture

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Abstract: Studies investigating behavioral distraction have found inconsistent results with significant cost (see Escera et al. 2000; Escera et al. 2003 for reviews), or benefit (see Parmentier 2014 for a review) in reaction times to targets when preceded by a so-called distracting sound. These results suggest that distracting sounds would not only trigger a detrimental attentional capture but could also produce a facilitation effect. We investigated the impact of unexpected salient sounds on the processing of a target sound, by manipulating the delay between the two sounds. We could evidence that distracting sounds trigger several phenomena that produce opposite effects on the reaction time to a subsequent target: a cost by an attentional capture mechanism, and a benefit due to an increase in arousal. Moreover, the analysis of the event-related potentials revealed that (1) increasing task load in top-down attention reduces early processing of the distracting sound (N100 and early frontal P3), but not bottom-up attentional capture mechanisms indexed by the late P3 response, (2) the bottom-up attentional capture by distracting sounds on target processing results in a delayed latency of the N100 sensory response to target sounds mirroring increased reaction times. Further analysis showed that the early frontal P3 amplitude is related to the arousal content of the distracting sounds and may index the arousal increase triggered by these sounds. Therefore, this work provides evidence for different mechanisms triggered by unexpected salient sounds both at the behavioral and electrophysiological levels.

Disclosures: A. Bidet-Caulet: None.

Poster

819. Human Cognition: Attentional Networks

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Title: A human brain network linking arousal to awareness

Authors: *D. B. FISCHER[1,2], A. BOES[1,3], A. DEMERTZI[4,5], H. C. EVRARD[6,7], S. LAUREYS[5], B. EDLOW[8,9], C. B. SAPER[10], A. PASCUAL-LEONE[1,10], M. D. FOX[1,9,10], J. C. GEERLING[10];
[1]Berenson-Allen Ctr. for Noninvasive Brain Stimulation, Div. of Cognitive Neurology, Dept., Harvard Med. Sch. and Beth Israel Deaconess Med. Ctr., Boston, MA; [2]Harvard Med. Sch., Boston, MA; [3]Dept. of Pediatric Neurol., Harvard Med. Sch. and Massachusetts Gen. Hosp., Boston, MA; [4]Brain and Spine Inst. (Institut du Cerveau et de la Moelle épinière-ICM), Hôpital Pitié-Salpêtrière, Paris, France; [5]Coma Sci. Group, GIGA-Research & Cyclotron Res. Ctr., Univ. and Univ. Hosp. of Liège, Liège, Belgium; [6]Functional and Comparative Neuroanatomy Lab., Ctr. for Integrative Neurosci., Tübingen, Germany; [7]Max-Planck Inst. for Biol. Cybernetics, Tübingen, Germany; [8]Dept. of Neurol., Harvard Med. Sch. and Massachusetts Gen. Hosp., Boston, MA; [9]Athinoula A. Martinos Ctr. for Biomed. Imaging, Massachusetts Gen. Hosp., Charlestown, MA; [10]Dept. of Neurol., Harvard Med. Sch. and Beth Israel Deaconess Med. Ctr., Boston, MA

Abstract: OBJECTIVE: Arousal, or wakefulness, is a fundamental brain process on which all cognitive functions rely, and which has important clinical applications. However, the neurobiology of arousal in humans remains incompletely characterized. The underlying neuroanatomy can be studied through focal lesions that induce coma, with evidence suggesting that such lesions commonly involve the pontine tegmentum. However, the precise location of the brainstem region critical for arousal remains unclear. Furthermore, the brainstem is thought to promote arousal through ascending projections to a distributed network, but the nodes of this network in humans are poorly defined. METHODS: To identify the brainstem region critical for arousal and its associated network in humans, we integrated a lesion overlap analysis with resting state functional connectivity MRI (rs-fcMRI). We collected 36 focal brainstem lesions: 12 lesions caused coma, and 24 control lesions caused motor deficits with preservation of

consciousness/arousal. By overlapping the coma lesions and subtracting the control lesions, we identified a coma-specific region of the brainstem. We then used rs-fcMRI collected from 98 healthy individuals to identify the functionally connected network of this coma-specific region. RESULTS: The coma-specific region of the brainstem localized to the lateral pontine tegmentum, overlying the medial parabrachial nucleus (PB). The rs-fcMRI analysis revealed two functionally connected nodes: the agranular insula (AI) and anterior cingulate cortex (ACC). These regions exhibited significantly more connectivity to coma lesions than control lesions. Based on connectivity to the AI and ACC, the PB most closely resembled the coma-specific region, compared to other nearby nuclei. CONCLUSIONS: Coma-causing lesions appear to involve the PB, which exhibits connectivity to the AI and ACC in a three-node network. Damage to the PB region may therefore be integral to the pathophysiology of coma; as the PB is critical to arousal in non-human animals, our findings suggest a homologous neural system of arousal between animals and humans. The AI and ACC are the primary sites of Von Economo neurons, and have been implicated in conscious awareness in humans. Our findings therefore link a brainstem nucleus of arousal to cortical regions associated with human awareness, offering a neural basis for integration of these two processes.

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Poster

819. Human Cognition: Attentional Networks

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Support: NSF Grant 0094992

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Title: Increase in the brain's functional small-worldness with the capture of attention

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[1]Psychology, [2]Vanderbilt Vision Res. Ctr., [3]Ctr. for Integrative and Cognitive Neurosci., Vanderbilt Univ., Nashville, TN

Abstract: The initial presentations of salient, task-irrelevant unexpected events can powerfully capture our attention, disrupting ongoing goal-directed behavior and transiently blinding us to other events (Asplund et al., JEP:HPP, 2010). Here, we tested the hypothesis that the extensive psychophysiological and cognitive changes associated with such attention capture are related to widespread changes in the brain's functional connectivity. Specifically, we used graph theory analysis combined with fMRI to characterize the large-scale community structure of functional connectivity data associated with the capture of attention by salient, task-irrelevant 'oddball' stimuli. Thirty participants were scanned while they searched for a target letter in a rapid serial visual presentation (RSVP) stream of distractor letters. Without warning to participants, oddball stimuli were presented during the search periods of six of the 40 trials. The presentation of these oddballs in the RSVP stream strongly captured attention and reduced detection accuracy of subsequently presented targets (Asplund et al., Nat Neurosci, 2010; Asplund et al., JEP:HPP, 2010), an effect that quickly attenuated with repeated oddball presentations. Functional connectivity between each region of interest (ROI) was assessed via pair-wise psychophysiological interactions (PPI) analysis (Mclaren et al., NeuroImage, 2012; Godwin et al., PNAS, 2015) in order to examine the interaction of connectivity seed and oddball processing. Cortical ROIs were defined using a published set of 264 coordinates (nodes) parsed into 14 identified cortical networks (Power et al., Neuron, 2011). Analyzed as a whole, the six oddball presentations produced an increase in functional modularity (measuring separability of cortical networks) and local efficiency (measuring functional distance between a node's neighbors), as well as an increase in the small-worldness of the cortical graph system driven by an increase in the clustering coefficient (measuring the number of recurrent triad connections between nodes). Importantly, the first two oddball presentations showed the greatest changes in modularity, local efficiency, clustering and small-worldness, while the later oddball presentations showed a shift towards graph metrics similar to those seen during search trials with no oddball presentations, mirroring the decrease in behavioral capture effects exhibited by repeated oddball presentations. These findings suggest that the powerful and extensive capture of attention by a salient, task-irrelevant event may result from rendering the brain's functional network connectivity a small(er) world.

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Poster

819. Human Cognition: Attentional Networks

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Support: Princeton Neuroscience Institute Innovation Fund

Title: Functional organization of the temporoparietal cortex

Authors: *K. M. IGELSTROM, T. W. WEBB, M. S. A. GRAZIANO;
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Abstract: The human temporoparietal junction (TPJ) is a topic of intense research. Imaging studies have identified TPJ activation in association with many higher-order functions, such as theory-of-mind, episodic memory and attention, causing debate about the distribution of different processes. One major challenge is the lack of consensus about the anatomical location and extent of the TPJ. Here, we address this problem by using data-driven analysis to test the hypothesis that the bilateral TPJ can be parcellated into subregions. We applied independent component analysis (ICA) to task-free fMRI data within a local region around the bilateral TPJ, iterating the ICA at multiple model orders and in several datasets. The localized analysis allowed finer separation of processes, and the use of multiple dimensionalities provided qualitative information about lateralization. We identified four subdivisions that were bilaterally symmetrical and one that was right-biased. To test whether the independent components (ICs) reflected true subdivisions, we performed functional connectivity analysis using the IC coordinates as seeds. This confirmed that the subdivisions belonged to distinct networks. The right-biased IC was connected with a network often associated with attentional processing. One bilateral subdivision was connected to sensorimotor regions and another was connected to auditory regions. One subdivision that presented as distinct left-biased and right-biased ICs was connected to frontoparietal regions. Another subdivision that also had left- and right-biased ICs was connected to social or default mode networks. Our results show that the TPJ in both hemispheres hosts multiple neural processes with connectivity patterns consistent with well-developed specialization and lateralization.

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Poster

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Support: Italian Ministry of Health: grant RF10.091

University "La Sapienza" - Progetto Ateneo 2012

Title: Selective reorienting response of the left hemisphere to invalid visual targets in the right side of space

Authors: *F. DORICCHI[1,2], M. SILVETTI[5], A. DRAGONE[3,6], S. LASAPONARA[6], E. MACALUSO[4];
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Abstract: In a recent fMRI study [1] we have highlighted anatomically overlapping though functionally separated BOLD responses to invalid and valid targets in the TPJ and IFG areas of the left hemisphere. Previous studies have usually compared directly the BOLD responses between invalid and valid targets, thus leading to the reciprocal cancellation of these functionally different responses in the left hemisphere [2]. On the contrary we have showed that when BOLD responses to invalid targets are compared to those evoked by neutrally cued ones, clear activations in the left TPJ and IFG are found. This suggests a role of the left hemisphere in reorienting. Based on this evidence, in two fMRI studies we have re-investigated: a) the preference of the two hemispheres in reorienting attention to the left and the right side of space; b) whether the overlapping responses to invalid and valid targets in the left hemisphere are generated by functionally segregated populations, i.e. MPVA of the BOLD signal. The results of these two investigations show that: a) the left hemisphere reorients attention only to the right side of space while the right hemisphere toward both sides of space; b) the responses of the left TPJ and IFG to invalid and valid targets are generated by functionally segregated populations. These findings provide the first fMRI evidence supporting the hypothesis that the higher incidence of contralesional neglect after right brain damage is linked to the preferential reorienting response of the left hemisphere to events occurring in the right side of space [3, 4]. 1. Doricchi, F. et al. Cerebral Cortex, 20(7), 1574-1585 (2010); 2. Corbetta M. et al. Neuron, 58(3), 306-324 (2008); 3. Mesulam, M. Annals of neurology, 10(4), 309-325. (1981); 4. Heilman K M. & Van Den Abell T. Neurology, 30(3), 327-330 (1980).

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Poster

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Topic: F.01. Human Cognition and Behavior

Support: NIH Grant EY021644

NSF Grant BCS- 1059523

Title: Visual field asymmetries reflect the retinotopic nature of parietal cortex

Authors: *S. L. SHEREMATA[1], G. L. MALCOLM[2], S. SHOMSTEIN[3];
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Abstract: Visual attention (Sheremata & Silver, 2015) and short-term memory (Sheremata, Bettencourt, & Somers, 2010) modulate posterior parietal representations of the visual field. With increasing task demands, right, but not left parietal cortex representations reflect spatial locations across the visual field. As predicted by these hemispheric asymmetries, memory performance varies across the visual field according to task demands (Sheremata & Shomstein, 2014). In order to link visual field biases directly to parietal activity, it is necessary to show that such biases reflect properties of the parietal cortex. One such property, retinotopic organization, predicts that visual field asymmetries should be eye-position dependent. In a set of experiments, this assumption was tested by monitoring eye position while subjects performed a color change-detection task. Memory items were presented on the left or right side of the monitor while subjects fixated either the center of the screen (control condition) or locations peripheral to the stimuli. If visual field biases reflect retinotopic representations in the parietal cortex, performance should reverse when subjects fixate peripheral visual field locations. Results demonstrated that visual field asymmetries occur in retinotopic coordinates, as evidenced by a reversal of visual field asymmetries in the peripheral fixation condition compared to the control condition. Further manipulations revealed visual field asymmetries even when stimuli were presented sequentially at a single location and therefore could not be maintained in retinotopic coordinates, suggesting that visual field biases do not solely reflect maintenance of visual information. These results demonstrate that visual field asymmetries reflect underlying neural constraints and can be used to estimate asymmetries in the brain.

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Poster

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Support: NIH R01 EY022229

NSF CELEST SMA-0835976

NIH 1F31MH101963-01

Title: Auditory and visual biases in 'multiple-demand' regions of human lateral frontal cortex

Authors: *A. L. NOYCE[1], S. W. MICHALKA[2], B. G. SHINN-CUNNINGHAM[2], D. C. SOMERS[1];
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Abstract: Lateral frontal cortex (LFC) is often characterized as domain-general or multiple-demand, due to its recruitment in a wide range of cognitive tasks (e.g. Duncan 2010; Fedorenko et al., 2013). We have previously used fMRI to identify discrete interleaved structures within LFC that show a preference for sensory modality during attention tasks (Michalka et al.). Here, we performed a replication test of that finding, and further investigated the sensory-biased versus multiple-demand nature of these regions. In our first experiment, we compared auditory to visual selective spatial attention. Subjects (n = 10) monitored one of two visual and two auditory stimulus streams for digits interspersed among letters. In our replication experiment, we compared auditory to visual nonspatial working memory. Subjects (n=14) performed visual 2-back (faces) and auditory 2-back (animal calls) tasks. In a direct contrast of auditory to visual task activations, both experiments identified four bilateral interdigitated regions with significant sensory modality preferences in a majority of subjects. Visual-biased superior precentral sulcus (sPCS) and inferior precentral sulcus (iPCS) alternate with auditory-biased transverse gyrus intersecting precentral sulcus (tgPCS) and caudal inferior frontal sulcus (cIFS). In the subjects who participated in both experiments (n = 7), the locations of these sensory-biased frontal lobe regions were stable over the >1 year between scans. We defined a broad lateral frontal cortical ROI in each hemisphere that encompassed all four of these structures as well as adjacent areas of LFC, and identified vertices that were significantly activated in either 2-back task (vs. passive). Approximately 25% of these vertices were activated only by visual working memory, 25% only by auditory, and 50% were significantly activated in both tasks (multiple-demand). Roughly half of these multiple-demand vertices showed a strong bias towards either the visual (36%) or auditory (19%) 2-back task. Therefore, a substantial majority of the LFC vertices that were activated in either the visual or auditory 2-back tasks exhibited a bias for sensory modality; only about 25% were activated to a similar degree in both tasks. These findings help to reconcile our

report of strong LFC bias for attended sensory modality with prior findings of multiple-demand responses in LFC: multiple-demand and sensory-biased functioning are not mutually exclusive characteristics. LFC is likely multiplexing multiple sources of information in order to support flexible responses to a rich sensory environment.

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Poster

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Title: Modulation of intracranial field potential responses during a spatial attention task reveals a functional hierarchy of processing in the human attention network

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Abstract: Spatial attention is mediated through a large-scale network that includes occipital, temporal, parietal and frontal cortical regions. While the network architecture has been well characterized using neuroimaging methods, less is known about the temporal dynamics in local regions and across the network. Here, we explored the modulatory effects of spatial attention throughout this cortical network by analyzing intracranial field potentials recorded from 729 ECoG electrodes implanted in 8 epilepsy patients. We examined the effects of attention using a variant of the Eriksen flanker task, where subjects had to differentiate between two shapes. An explicit cue indicated the spatial location of an upcoming target shape which, after a variable delay period, was presented embedded in a circular array of shapes. Specific cue-related broadband high frequency activity indicated constrained response fields in 70 electrodes (10%). We examined response modulation from those electrodes during the delay period of the task when subjects either attended to or away from the response field. We found that covert spatial attention differentially affected low frequency (4-30Hz) and broadband high gamma (50-200Hz) power during the delay, with specific profiles that developed through the delay period. Delay activity was sustained with attention across the network, with the duration of the activity shortest in visual compared to parietal and then frontal areas. We used the temporal progression of these responses to develop a functional hierarchy of activity along the dorsal pathway through nodes of the fronto-parietal attention network, from V1 through intraparietal sulcus areas IPS0-IPS5 and the frontal eye fields.

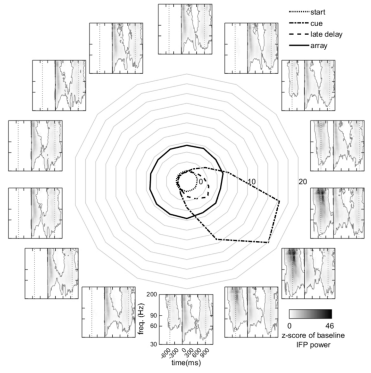

Figure 1. Example broadband high frequency selectivity during the cue and delay periods from an electrode implanted over left visual cortex. Time-frequency spectrograms show z-scored power relative to baseline (300ms prior to trial start) for trials cued at each location, aligned to array onset (0ms). Contours indicate clusters of significant activity compared to baseline ($p<0.001$, corrected for multiple comparisons). Inset polar plot shows for each cue location the mean z-score of high frequency power (70-170Hz) in the 300ms following the trial start (dotted), cue (dot-dash), and array (solid). Late delay activity is shown (dashed) for the 300ms prior to array onset. Note the significant cue and delay selectivity in the lower-right quadrant.

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Poster

819. Human Cognition: Attentional Networks

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Title: Frontoparietal determinants of visuospatial attention

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Abstract: Background: Selective attention facilitates neural processing of attended information at the expense of irrelevant or distracting inputs. To this end, selective attention relies on a number of mechanisms, like gain-control, oscillatory synchrony and selective entrainment, which are coordinated by the Frontoparietal Attention Network (FPAN). While much recent inquiry clearly supports a direct role for the FPAN in the deployment of attentional mechanisms like alpha oscillations and selective entrainment, the mechanisms underlying this deployment remain largely ambiguous. Also relatively unexplored is the relationship between attentional indices and the FPAN's white matter structure. Methods: Our work pairs the temporal resolution of electroencephalography (EEG) with magnetic resonance imaging (MRI) methods to reveal the nuanced relationships between the structural anatomy of the FPAN, the FPAN's temporal dynamics, downstream deployment of attention (indexed by occipital alpha oscillations and selective entrainment), and behavioral performance. Specifically, these relationships are characterized in the context of a sustained visuospatial attention task with rhythmic visual stimulation. Results: EEG evidence suggest that bilateral Frontal Eye Fields (FEFs; nodes of the FPAN) selectively entrain to rhythmic environmental stimuli. Additionally, entrainment over frontal electrode sites significantly correlates with Fractional Anisotropy (FA) of the right Superior Longitudinal Fasciculus (rSLF), indicating that this white matter tract plays an important role transmitting rhythmic attended information from occipital to frontal lobes. Lastly, selective entrainment shapes the temporal profile of ongoing activity in the alpha band (8-12 Hz) over occipital electrodes. Specifically, cross-frequency coupling is observed as a result of attention to a rhythmic stimulus. Conclusion: Entrainment of task-related neural networks to environmental stimuli may aid attempts to dissect their dynamics. The analysis presented here highlights structural and functional characteristics of the FPAN that predict task performance across individuals. Further, as it appears that that the structural characteristics of the FPAN correlate with EEG metrics of network-level activity, we hope this work will pave the way for development of non-invasive biomarkers of FPAN function for eventual clinical use in assessing disease-related risk and impairment and to monitor rehabilitation and recovery of FPAN function.

Disclosures: **T.J. Wilson:** None. **J.J. Foxe:** None.

Poster

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Topic: F.01. Human Cognition and Behavior

Title: Voxel-wise functional connectivity profiles support task-demand specific network motifs in multiple demand region "Inferior Frontal Junction" (IFJ)

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Abstract: A multitude of fMRI studies confirms the existence of a dedicated brain network for the execution of attention demanding task. A subset of nodes in this network exhibit the multiple demand characteristic: their activity is modulated by cognitive effort, regardless of the specific task demands. How this characteristic emerges is yet unknown. Recently, we showed that voxels within multiple-demand nodes exhibit consistent task preference profiles and therefore do distinguish between different task demands (Stiers ea NeuroImage 52:252). Moreover, voxels with similar task preferences throughout the multiple demand network show stronger functional coupling during execution of preferred and non-preferred tasks. This suggests that different task demands are processed in the network by parallel subnetworks of anatomically interconnected neuron population. A reason of existence for such subloops in multiple demand nodes could be that loop-constituting cell groups connect to different brain structures outside the network, engaged by different task demands. We used voxel-wise functional connectivity analysis in 10 healthy adult participants to investigate this hypothesis. Participants performed alternating short blocks of back-matching, response switching and flanker interference in a 3 Tesla fMRI scanner. In two runs the difficulty level of the tasks was varied to identify co-activated voxel clusters with the multiple demand property. Our analysis focused on the inferior frontal junction (IFJ) node. In four additional runs only difficult blocks of the tasks were included to independently identify the task preference profiles of the IFJ multiple demand voxels. Lastly, for each IFJ multiple demand voxel the functional connectivity (FC) profile with the rest of the brain was computed from 10 minute unsmoothed resting state fMRI data. Analysis of voxel FC profiles revealed that FC similarity (eta^2) between same preference voxels was significantly higher than between different preference voxels in the same cluster (with matched inter-voxel distances) in 10 of 10 participants, and between interhemispheric voxels in 8 of 10 participants. Moreover, whole brain

GLM analysis of FC maps averaged per participant and task preference revealed unique FC patterns associated with each task preference voxel class over participants. These results support the notion that separate subpopulations of neurons within IFJ bind different brain structures to the multiple demand node, depending on the specific demands imposed by a task. Moreover, they provide insight into the mechanism of how motifs within a larger network can be assembled for particular task demands.

Disclosures: P. Stiers: None. **A. Goulas:** None.

Poster

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Topic: F.01. Human Cognition and Behavior

Title: Examining network connectivity associated with the Sustained Attention to Response Task

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Abstract: A key objective of cognitive neuropsychology is to examine the neural architecture underlying cognitive function. Advances in neuroimaging techniques show that adequate cognition requires recruitment of an interconnected network of brain regions. Until recently, however, it was difficult to obtain a concise quantification of the extensively interconnected human brain. To meet this limitation, neurophysicists have proposed a model of network connectivity in which topological measures based on Graph Theory can be applied to quantify complex networks of the brain. These network metrics examine the global network architecture of the brain by quantifying measures of local connectivity between cortical regions, characterizing network efficiency and identifying significant hubs of the network. Surprisingly, only a small number of studies have applied network theory to explore the network connectivity associated with cognition, and its resilience. Our study aimed to quantify network metrics associated with cognition and examine whether network analysis is sensitive to the network differences associated with cognition. We administered the Sustained Attention to Response Task (SART) to 29 healthy controls while simultaneously measuring electroencephalography (EEG). Our first objective was to examine whether the globally emergent network properties of the baseline condition (no task) differ from the effortful task condition. Our second objective was

to explore whether the network analysis could identify different network dynamics associated with the GO condition (sustained attention) relative to the NOGO condition (response inhibition). Our study demonstrated that at baseline there was a significant dampening of network metrics reflecting a less connected and global efficient network relative to the effortful task conditions. Within the effortful task condition, the GO condition was represented as a more connected, globally-efficient and resilient network than the NOGO condition. Additionally, the topological distribution of the network metrics (mean degree and clustering coefficient) was increased around frontal and parietal areas in the GO condition relative to the NOGO condition, while the NOGO condition was increased around central electrodes. Given these network metrics and the topological measures, we suggest that sustained attention relies on a widely distributed and globally efficient network, while response inhibition relies on a smaller but more centralized network dynamics. Therefore, network analysis is emerging as a useful tool for the quantification of the global networks that are fundamental for cognitive function.

Disclosures: J. Naim-Feil: None. **E. Moses:** None. **M. Rubinson:** None. **N. Levit-Binnun:** None.

Poster

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Title: DMN function, attention shifting and attention holding compared across humans and monkeys

Authors: *N. S. CASPARI[1], R. VANDENBERGHE[2,3], W. VANDUFFEL[1,4,5];
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Leuven, Belgium; [4]Harvard Med. Sch., Boston, MA; [5]MGH Martinos Ctr. for Biomed. Imaging, Charlestown, MA

Abstract: A unifying function of the default mode network (DMN), activated during rest compared to active task conditions in human and monkey has been difficult to define. In humans, it is engaged during internal modes of high level cognition. However, this DMN definition is difficult to sustain in other animal species such as monkeys or rats. As an answer to this, it has recently been proposed that, at least in monkeys, attention shifts trigger activation of posterior DMN areas (SFN 2014, Abstract nr. 11931). Here we aimed to assess to which degree shifts in spatial attention may explain DMN function in human, by comparing attention shift and default mode networks within and across species. Monkeys (N=3) and humans (N=22) performed the same covert selective attention task in the MR scanner, with interleaved periods of shifts and sustained attention (Caspari et al., 2015; Molenberghs et al., 2007). Two pairs of shapes were presented on the horizontal meridian (9.25 deg) and each pair contained a relevant and irrelevant shape. Subjects fixated centrally and responded manually when the relevant stimulus dimmed. An event consisted of the replacement of the current stimulus pair by the next. In 1/3 of the trials, this change elicited a spatial shift in attention as the relevant stimulus was replaced by an irrelevant one. Monkeys were scanned (1.25 mm isotropic) using MION contrast agent, and humans were scanned measuring BOLD (2.75 x 2.75 x 3.5 mm) in a 3T MR scanner. In monkeys, a mixed effects analysis revealed a high degree of overlap (>70%) in cortex posterior to the central sulcus (CS), between shift-related activations and the monkey DMN as defined by Mantini et al. (2011) (comparing rest vs. active task conditions in 15 experiments). In contrast, shift-related activations anterior to the CS overlapped marginally with the DMN (8.15%). In human, a random effects analysis revealed an overlap of 27% posterior to the CS, between shift-related activations and the DMN defined by Laird et al. (2009), using a meta-analysis of an activation likelihood estimation on 1711 neuroimaging publications. Similarly as in monkey, overlap in frontal cortex was small (3%). Sustained contralateral attention, compared to the DMN, activated an entirely different set of areas in both species, except for lPFC, portions of ACC and IPS in monkey. Our results indicate a functional subdivision of the DMN in both species whereby the posterior but not anterior DMN overlapped with shift but not sustained attention activations. The smaller percentage of the posterior DMN core activated for shifting in humans is in line with a large expansion of this part of cortex and, likely, an additional gain of function as compared to monkeys.

Disclosures: **N.S. Caspari:** None. **R. Vandenberghe:** None. **W. Vanduffel:** None.

Poster

820. Cognition and Behavior: Human Working Memory

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Topic: F.01. Human Cognition and Behavior

Title: Examining the effects of long-term high-intensity aerobic training on behaviors associated with the prefrontal cortex, hippocampus and striatum using electroencephalography

Authors: *J. C. BASSO, C. CROSTA, T. R. LEE, A. MCHALE, N. PAYNE, S. SHEN, N. SINGH, W. A. SUZUKI;
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Abstract: Long-term voluntary exercise in rodents causes anatomical, physiological and behavioral changes in a variety of brain regions, namely the hippocampus (Hpc), striatum (Str) and prefrontal cortex (Pfc). Investigations of exercise-induced improvements in cognition in humans have focused on the Pfc, and few studies have sought to determine the electrophysiological correlates of such changes. In this randomized controlled trial, we examined the effects of long-term aerobic exercise on behaviors associated with the Pfc, Hpc, and Str at both a behavioral and electrophysiological level. Healthy, low-fit male and female subjects, ages 35 to 59, were randomly assigned to participate in high-intensity aerobic exercise (indoor cycling) or video gaming for 3 months. Each subject participated in three 45-minute exercise or video game sessions per week. Before and after this intervention, subjects were tested on a variety of neuropsychological tests that tapped the functioning of various brain regions while having their brain activity recorded through electroencephalography (EEG). These computer-based tasks included the Stroop Task, Reading Span Task, N-back Task, Spatial Navigation Task, Behavioral Pattern Separation Task, Pursuit Rotor Task, and Probabilistic Learning Task. Changes in mood and psychological state were also assessed through a variety of questionnaires administered before and after the intervention. Heart rate was captured during the majority of exercise and video game sessions and cardiopulmonary functioning was measured through maximal oxygen capacity (VO2 max) assessment at both pre- and post-intervention testing sessions. We predict that compared to their sedentary counterparts (video game subjects), those subjects engaged in the exercise intervention will show enhanced behavioral functioning in these brain-region specific tasks. Furthermore, those individuals that show greater enhancements in their cardiopulmonary functioning will show greater behavioral improvements. Through time-frequency and phase-amplitude coupling analysis of the EEG data, we predict that exercise will enhance alpha, beta and theta oscillations as well as coherence between low frequency bands and gamma during rest and cognitive challenge. Data is currently being collected (complete: n=3 exercise, n=4 control; enrolled: n=15 exercise, n=9 control), with a goal of n=66 (33 subjects per group) in total. At the beginning of the intervention, VO2 max scores were equivalent ($p>0.05$; mean = 16.73; SEM = 1.16). Exercise subjects expended an average of 542.2±25.48 calories per workout, resulting in an increase of up to 2.4 ml/kg/min over the 3-month period.

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Poster

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Title: Individual differences in alpha power modulation by verbal working memory load

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Abstract: During retention of verbal working memory, posterior alpha power is increased monotonically with memory load, providing a mechanism of proactive distractor suppression. In this study we investigated the individual differences in the modulation of alpha power by verbal working memory load. High density EEGs (128 channels) were recorded while healthy volunteers performed a modified Sternberg working memory scanning task. Seated in an acoustically and electromagnetically shielded chamber, the subject was shown a set of digits (0 to 9) on a CRT monitor for 1s. Following a 3s retention period, a probe digit was presented, and a “yes” (index finger in the dominant hand) or “no” (middle finger) button press was required to indicate whether the probe digit belonged to the set. Memory load was controlled by the size of the digit set which in this experiment was chosen to be 1, 3 or 5. Our main finding was that Cowan’s K as a measure of working memory capacity is negatively correlated with alpha power modulation. Specifically, the higher the working memory capacity, the less modulation of alpha by memory load. This finding suggests that subjects with lower WMC, being more susceptible to distractor interference, relies more on proactive mechanisms to suppress distraction.

Disclosures: **Z. Hu:** None. **I. Samuel:** None. **M. Ding:** None.

Poster

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Title: Adult-like resting state network connectivity but hyperconnectivity during visual working memory task in late childhood

Authors: P. JIANG[1,2], M. TOKARIEV[1,2], E. T. ARONEN[3], O. SALONEN[4], Y. MA[5], *V. A. VUONTELA[1,2], S. CARLSON[1,2];
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Abstract: Recent developmental neuroimaging studies on brain networks have focused on the resting state functional connectivity (Power et al., 2010; Dennis and Thompson, 2013), whereas little is known about the developmental changes in the brain networks engaged in cognitive tasks. In the current study, we used functional magnetic resonance imaging to investigate the large-scale brain network differences between healthy 7-11-year-old children (n = 16) and young adults (n = 13) during both resting state and visual 1-back working memory (WM) tasks. In the WM tasks, the memoranda were either face or scenery images. We used independent component (IC) analysis, a data driven analysis method, coupled with dual regression (Beckmann et al., 2009) and permutation tests (Winkler et al., 2014). Among the ICs that were found during resting state in children and adults, we identified the major resting state networks (RSNs) including visual, auditory, sensorimotor, salience, frontoparietal, and default mode networks (Damoiseaux

et al., 2006; Smith et al., 2009). During tasks, we found ICs corresponding to several task-related networks. The between groups comparison of brain networks showed that 7-11-year-old children have already established adult-like RSNs. However, during task performance, children exhibited significantly stronger connectivity than adults in several brain networks ($p < 0.05$, Bonferroni corrected for multiple comparisons) including networks related to the default mode, sensory processing and movement. We also found that a visual IC that included the spatial cognition-related brain regions - the parahippocampal place area and the restrosplenial complex (RSC) - exhibited equivalent synchronization in the two age groups during resting state. During task performance, however, the RSC showed stronger within network connectivity in children than adults. These observations demonstrate that in 7-11-year-old children, adult-like intrinsic brain networks are already established, but the configuration of the brain networks engaged in the WM tasks is still subject to dynamic maturational changes that occur over development.

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Poster

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Title: Constructing partial representation of objects in visual working memory

Authors: *J. SAIKI[1], Q. LI[2];
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Abstract: Visual working memory (VWM) maintains task-relevant features of objects and suppresses others, but flexibility in dimension-selective maintenance and its neural mechanisms remain unclear. The current study investigated dimension specific memory maintenance using a change detection paradigm, and its neural correlates in humans using electroencephalography (EEG). Participants memorized objects defined by colors, shapes, and locations, and detected a feature swap between objects. Successful detection of the feature swap required memory for the

feature conjunctions. Performance in a BASELINE condition where all three dimensions are task-relevant was compared with conditions where a swap in color, shape, or location was ignored (COLOR, SHAPE, and LOCATION conditions). Behavioral data revealed that LOCATION condition impaired performance, but COLOR and SHAPE conditions improved performance, suggesting that locations are indispensable to form VWM representations. The neural activity data showed that indices known to be correlated with memory load reflect different aspects of VWM representations. During the maintenance period, contralateral delay activity (CDA) was correlated with the behavioral impairment in the LOCATION condition, whereas frontal midline theta (FMT) amplitude was correlated with the behavioral improvement in the COLOR and SHAPE conditions. Posterior lateralized alpha amplitude was sensitive to the task demand of excluding irrelevant dimension, regardless of behavioral impairment or improvement. Behavior impairment and reduction of CDA amplitude in the LOCATION condition was specific to the attend-right condition, indicating left-hemisphere specific impairment, but no such hemispheric asymmetry was observed in the behavioral improvement and FMT increase in the SHAPE and COLOR conditions. This difference in hemispheric asymmetry also suggests functional dissociation between exclusion of spatial and non-spatial features. These results indicate that VWM can form and maintain partial representations of multidimensional objects, and neural indices reflect different structural aspects of these representations. In particular, spatial and non-spatial features play dissociable roles in the construction of partial representation of objects.

Disclosures: **J. Saiki:** None. **Q. Li:** None.

Poster

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Title: Attentional modulation of the contralateral delay activity (CDA) during working memory retention

Authors: ***D. CISLER**, M. N. JESSO, R. PARASURAMAN, P. GREENWOOD;
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Abstract: Interactions between attention and working memory (WM) are important for the fundamental cognitive processes involved in formation and retention of mental representations. We hypothesized that the role of visuospatial attention in WM involves enhancing the target figure and suppressing the ground. One prediction of this hypothesis is that a location precue closely encompassing the target of a WM task would result in a more accurate target mental representation andtherefore require less cortical activity to maintain target representation during the delay period. Cortical activity was measured in the contralateral delay activity (CDA), shown to index WM load (Vogel et al., 2005).On each trial,young adult participants (n=7) were first shown an arrow (300ms) above a fixation cross indicating which half of the screen they should attend. The arrow then disappeared and only a fixation cross was visible for 350ms before a bilateral rectangular bracket cue subtending 4.0 degrees, 6.5 degrees, or no cue, was presented for 500 ms.At cue offset, bilateral memory arrays consisting of 2 or 4 red and blue rectangleswere presented for 100 ms.Factors were memory load (2) and cue size (3). Following memory array offset, a 900ms delay interval began during which only the fixation cross was visible.Finally a test display appeared and participants made a speeded decision within 2 s indicating whetherthe test displaywas the same or different from the target.The CDA was calculated from PO3/PO4 difference waveforms and the voltage wasaveraged between 300-900 ms of the delay period. We found that as cues became more precise, the negative CDA became more positive (p=.09)andtarget discrimination RTbecame faster.The smaller CDA presumably reflectedthe amount of neural activity needed to maintain the mental representation during WM maintenance.Theseorderly findings suggest that the more precisely visuospatial attention isfocused on target location prior to encoding, the less neural activity is required to maintain the mental representation during the delay period.This is consistent with the hypothesized role of visuospatial attention in WM in enhancing target mental representation during WM maintenance.

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Poster

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UC Irvine School of Medicine Bridge Fund

Title: Characterizing frontal-medial activity in working memory with electrocorticography

Authors: *E. L. JOHNSON[1], S. M. SZCZEPANSKI[1], J. PARVIZI[2], J. J. LIN[3], R. T. KNIGHT[1];
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Abstract: Our ability to maintain and process information in an active state is a critical component of high-level cognition. While decades of research implicate the lateral frontal cortex as well as parietal, temporal, and/or occipital regions in neural networks that underlie working memory function, far less is known about the role(s) of frontal polar (FPC) and orbitofrontal (OFC) cortices, termed the frontal-medial network. Studies of FPC neurophysiology are uniquely limited because the most rostral region of the FPC is not developed in the closest non-human primates. We examined high-gamma (HG; 70-250 Hz) activity within frontal-medial regions using multi-modal electrocorticography (ECoG). ECoG yields data of unparalleled spatiotemporal resolution in human neuroscience, and that include an expanded range of frequencies over non-invasive electrophysiology. Importantly, HG activity has been linked to neuronal spiking and shown to represent individual stimuli in the cortex, and when coupled with low-frequency oscillations, may facilitate long-range information transmission. Subjects with subdural (n = 1) and/or depth (n = 3) electrodes maintained “what”, “where”, and/or “when” information online in preparation for an immediate test. They studied pairs of two colored shapes, presented one at a time in specific spatial and temporal positions. After a 900-ms maintenance period, they were given a test prompt - SAME (”what”), TOP/BOTTOM (”where”), or FIRST/SECOND (”when”) - and then a 900-ms processing period before indicating the response. We report the temporal dynamics of HG power during both 900-ms delay periods. In each subject, we found increases in HG power during processing compared to maintenance, consistent with findings that frontal-medial cells encode goals at the time of feedback. Two patterns of activity emerged during the processing period such that electrodes showed either information-selectivity or power increases irrespective of information type. All information-selective electrodes showed increased, transient HG power when subjects were processing “where” or “when” information, compared to “what” information. Furthermore, distinct subgroups of electrodes in a left FPC subdural grid revealed selectivity for “where” relative to “when” or “when” relative to “where” information. These “where”-selective electrodes were located in a relatively rostrolateral region, compared to “when”-selective electrodes, which were

dispersed in a more caudomedial array. We provide initial evidence of activity that is spatiotemporally distributed by information type within the frontal-medial network.

Disclosures: E.L. Johnson: None. **S.M. Szczepanski:** None. **J. Parvizi:** None. **J.J. Lin:** None. **R.T. Knight:** None.

Poster

820. Cognition and Behavior: Human Working Memory

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Topic: F.01. Human Cognition and Behavior

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Neuroscience Training Program T32-GM007507

Title: Working memory for visual motion in human areas MT and MST

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Abstract: How does the brain accomplish the short-term retention of visual motion? In the monkey, although the sample stimulus drives elevated spiking in area MT, this activity quickly returns to baseline during the delay period (e.g., Zaksas and Pasternak, 2006). Simultaneous recordings in three regions have revealed elevated delay-period spiking in dorsolateral PFC and in MST, and robust decoding of remembered direction of motion from these signals, as well as from the delay-period local field potential in MT (Mendoza-Halliday et al 2014). In the human, functional magnetic resonance imaging (fMRI) signal in "MT+" -- a region of interest (ROI) that does not differentiate MT from MST -- is phasically elevated to sample and probe stimuli, but returns to baseline during the delay, although multivariate pattern analysis (MVPA) decodes remembered information throughout the trial (Riggall and Postle, 2012), with a fidelity that predicts behavioral precision (Emrich, Riggall, et al. 2013). In the present study, we independently localized area MT and MST (Huk, et al., 2002). Subsequently we measured BOLD response during delayed recall for the direction of 1-sec samples of dots moving with

100% coherence in one of three directions. In a preliminary n of 5 subjects, fMRI signal intensity in the two regions showed comparable patterns of robust phasic responses to sample and probe events, and a return to baseline during the intervening delay period. MVPA decoding performance, above chance for both regions, was superior for MT. Thus, for the human, as in the monkey, the physiological bases of the short-term retention of motion information may differ between MT and MST.

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Poster

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Support: NIH R01MH095984

Title: Delay-period activity of the parietal cortex depends on working memory load, not interference

Authors: ***M. J. STARRETT**[1], O. GOSSERIES[2], J. J. LAROCQUE[3], E. SAAD[2], N. COWAN[4], B. R. POSTLE[1,2];
[1]Psychology, [2]Psychiatry, [3]Med. Scientist Training Program, Univ. of Wisconsin-Madison, Madison, WI; [4]Psychological Sci., Univ. of Missouri-Columbia, Columbia, MO

Abstract: One of the striking findings to come out of recent multivariate pattern analysis (MVPA) studies of visual short-term memory (VSTM) and working memory is that elevated delay-period activity - long considered a correlate of the storage of information - often does not carry stimulus information. In some parietal regions, including the intraparietal sulcus, signal intensity and MVPA both instead reflect working memory load. Here, we tested two competing, current accounts of this activity using functional magnetic resonance imaging (fMRI). One hypothesis is that load-sensitive increases in fMRI signal correspond to increased inhibition among mental representations. A second is that this activity reflects the increased demands on the selection mechanisms of a domain-general attentional system, such that more activity is required to select and sustain attentional prioritization with each additional item that is added to the load. To adjudicate between increased-inhibition and increased-selection accounts, we compared patterns of activity associated with increasing load via the number of items within the same stimulus category versus increasing load via items drawn from different categories. On

load 1 trials, subjects viewed an aperture in which a group of dots moved coherently. On within-category load-3 trials, three directions of motion were presented serially; on between-category load-3 trials, one direction of motion and two colored circles were presented serially (and, across trials, in different order). On all trials, the recall probe appeared as a virtual dial with the digit at the middle of the dial indicating which item to recall ("1", "2", or "3") by rotating the needle to indicate either the recalled direction of motion or the appropriate location on a color wheel. Behavioral estimates of mnemonic precision for the direction of motion were highest on load-1, markedly lower on between-category load-3 trials, and lower-still on within-category load-3 trials. These findings are consistent with our expectation that within-category load-3 trials would generate more inter-item interference. MVPA of activity from MT+ and more posterior visual regions indicated that the fidelity of the neural representation of the critical direction of motion dropped markedly between load 1 and the load 3 conditions, but did not differ between the latter two. Delay-period signal intensity in parietal cortex also showed the expected load sensitivity, but, critically, with the highest signal for between-category load-3 trials. These findings suggests that this region supports an operation that is insensitive to inter-item interference/inhibition.

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Poster

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Support: Air Force Research Laboratory contract FA8650-11-C-6157

Title: Modeling current density distribution for transcranial direct current stimulation: effect of conductivity

Authors: *M. S. SHERWOOD[1,2], J. H. KANE[1,3], M. P. WEISEND[1,2,3];
[1]Wright State Res. Inst., Beavercreek Township, OH; [2]Biomedical, Industrial, and Human Factors Engin., [3]Neuroscience, Cell Biology, and Physiol., Wright State Univ., Dayton, OH

Abstract: The effectiveness of transcranial direct current stimulation (tDCS) is likely dependent on the intensity and direction of current through the cortex. Finite Element Method (FEM) models are used make predictions regarding the brain regions that will be stimulated in tDCS. FEM models are limited by the detail and accuracy of tissue segmentation as well as

conductivity values assigned to each tissue compartment. FEM's have progressed from simple concentric spheres to magnetic resonance imaging (MRI) based realistic models. However, a wide range of conductivity values has been reported in the tDCS modeling literature. To our knowledge, there has not been a report demonstrating the impact of this variance on the distribution of current density in FEM models. A discrete anatomical model derived from a high-resolution MRI was obtained from BrainWeb. The number of compartments of this model, subject 18, was reduced to 7 isotropic compartments and manually corrected. Two electrode pads each modeled as 2x2x0.2 cm^3 were positioned on the scalp (anode-C3 and cathode-right supraorbital) and a FEM model was generated. Current distributions were calculated with tissue conductances from four previous publications assigned to the compartments within the FEM. The conductivity of air and blood were maintained at 1e-15 and 0.67 S/m, respectively. Inward normal current density (2 mA total) was applied to the exposed surface of the anode, ground to that of the cathode, and all other external surfaces were electrically insulated. Model 1 (M1) served as the baseline for computing differences in percent change in current density magnitude and orientation. M1 and M2 showed a large variation in current density magnitude on the GM surface. However, orientation changes varied across all three models. The changes in the current density were primarily under the electrode site. In contrast, the changes in orientation impacted spatially disparate regions of cortex and interacted with gyro folding. At present interventions are being designed with FEM models, each model potentially suggesting different electrode montages. The conductivity values, model detail, and accuracy of segmentation should be either uniquely determined or standardized to developed accurate, realistic models.

Conductivity (S/m) of FEM tissue compartments.

	M1	M2	M3	M4
Scalp	0.465	0.43	0.33	0.43
Bone	0.01	0.015	0.008	0.01
CSF	1.65	1.8	1.79	1.79
GM	0.276	0.10	0.33	0.33
WM	0.126	0.38	0.15	0.14
Electrode Pads	1.4	1	2	1.4

Disclosures: **M.S. Sherwood:** None. **J.H. Kane:** None. **M.P. Weisend:** None.

Poster

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Support: EU FP7 (Grant agreement 604102)

Foundation Adelis

Title: A synaptic theory of limited capacity of working memory

Authors: Y. MI[1,2], *M. V. TSODYKS[1];
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Abstract: Working memory (WM) refers to the short-term storage of stimulus information for the purpose of processing a cognitive function. Cowan summarized the experimental evidence that human subjects can only memorize about four different chunks in a WM task. However, the neural mechanisms underlying the limited capacity of WM remain largely unknown. Recently, we proposed a synapse-based theory for short-term information storage in a neural circuit. In this model, memory is retained in the facilitated recurrent connections between neurons, as opposed to the conventional mechanism relying on persistent neural responses to encode information. Here, we investigate how this information storage mechanism restricts the capacity of WM. We consider a neural circuit, which consists of multiple excitatory neural clusters and an inhibitory neuron pool. Each excitatory neuron cluster represents a specific memory item, and its activation signals the recall of this item. All clusters are connected to the inhibitory neuron pool, so that their activities compete with each other and hence only one item can be recalled at any given moment. Within each excitatory cluster, neurons are strongly connected with each other and their synapses exhibit short-term synaptic plasticity. Meanwhile, all excitatory neurons receive a constant background input, reflecting the arousal signal when the neural system is engaged in a WM task. When a single cluster receives a brief excitatory input pulse (loading of the corresponding memory item into WM), it generates a population spike (PS); if furthermore the concurrent background input is strong enough (a strong arousal level), the neuron cluster dynamics falls into a periodic state, so that the memory item can be reactivated repeatedly. When several items are loaded sequentially, the corresponding neuron clusters coordinate their dynamical behaviors to generate PSs cyclically. The memory capacity of the system is therefore the maximum number of PSs that can be accommodated in the periodic activity state of the network. Our analysis and simulations show that WM capacity of the model depends chiefly on the parameters characterizing short-term synaptic plasticity and inter-cluster recurrent

connections. Moreover, for realistic choice of parameters, we found that our model is compatible with empirically obtained WM capacity.

Disclosures: **Y. Mi:** None. **M.V. Tsodyks:** None.

Poster

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Title: Evoked responses and alpha oscillations reflect the top-down modulation of working memory representations

Authors: ***S.-J. LIM**, M. WÖSTMANN, J. OBLESER;
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Abstract: Selective attention is known to facilitate perceptual encoding of task-relevant stimulus into working memory (WM). Such facilitation is reflected in modulations of evoked potential responses and neural oscillations, especially in alpha frequency band (8-12 Hz), both serving as neural markers of attention-related perceptual processing and WM load. However, little is known about a beneficial role of selective attention directed towards objects maintained in WM: whether the orientation of attention to objects in WM improves representational quality of auditory WM and whether the attention-related neural correlates play specific roles in top-down modulations of representations held in memory. Using electroencephalography, we here investigate the underlying neural mechanisms of selective attention to auditory WM, in a syllable-pitch discrimination task with retroactive cues. On each trial, human listeners (N=20) encoded two distinct, sequentially presented syllables that were equally task-relevant. In some trials, a valid retro-cue was presented during the retention period to indicate which of the syllables in WM would be probed at the end of the trial. Other trials provided an uninformative neutral cue. Directing attention to specific syllable objects in WM in the valid cue trials led to faster responses and improved detection of precise acoustic change in the attended syllable. This benefit from selective attention to auditory WM objects was reflected in neural modulations of both evoked potentials and alpha oscillatory power. First, a sustained negative response during the retention period following the retro-cue was enhanced in amplitude. The extent of this

amplitude modulation predicted the behavioral benefits from a valid versus neutral cue quantified as perceptual sensitivity (d'). Second, compared to the neutral retro-cue, the valid cue induced suppression of centro-parietal alpha power. The extent of this alpha power suppression predicted inter-individual differences in precise recall of syllables maintained in WM. In sum, our results suggest that selective attention to auditory WM objects improves the representational quality of objects in WM. The extent to which participants benefit from directing attention to specific WM objects is predicted by modulations of evoked responses and alpha power.

Disclosures: S. Lim: None. **M. Wöstmann:** None. **J. Obleser:** None.

Poster

820. Cognition and Behavior: Human Working Memory

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Support: AFOSR Grant FA9550-10-1-0385

Title: Working memory in mouse and man: novel genetic variants in the formiminotransferase cyclodeaminase (FTCD) gene identified in mice and assessed in humans

Authors: *K. D. SCHMIDT[1], R. JANKORD[1], M.-K. LIN[2], R. LIPSKY[2], R. PARASURAMAN[2], P. M. GREENWOOD[2];
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Abstract: Working memory (WM) is important for real world cognitive functioning. Knowledge of specific genes modulating WM performance can be informative about underlying molecular mechanisms of memory formation and retention. WM has been found to be highly heritable (Ando et al., 2001). However, the only cognitive measure investigated in a genome-wide association study (GWAS) used IQ as a phenotype and found no single nucleotide polymorphisms (SNPs) reaching genome-wide significance (Davies et al., 2011). The GWAS approach is impractical for investigating the genetics of WM as large samples with required phenotypic information do not exist. Using a candidate gene approach, WM performance has been associated with several genes (e.g. Greenwood et al., 2014). However, a less biased approach is sought. We investigated the gene encoding the enzyme formiminotransferase cyclodeaminase (FTCD), the autoantigen recognized by anti-liver cytosol type 1 (LC1) autoantibodies in type 2 autoimmune hepatitis (AIH) patients. Its role in the biosynthesis of the neurotransmitter glutamate is not well understood. FTCD was hypothesized to modulate working

memory in humans based on Quantitative Trait Locus mapping of BXD mice for Morris Water Maze performance (Shea et al., 2013). The Allen Human Brain Atlas shows robust mRNA levels for the FTCD gene in the caudate, putamen, and globus pallidus, as well as the dentate gyrus. In a large sample of healthy people, we examined two SNPs in the FTCD gene, rs914246 and rs914245. These SNPs were selected based on clinical significance reported in the literature, minor allele frequency, SNP location on the promoter region of the FTCD gene, and potential for effects on microRNA binding sites. 790 healthy males and females, ages 17 - 90, participated in a delayed match-to-sample task manipulating memory load (1, 2, or 3 target locations) and discrimination difficulty (same or different location 2°, 4°, or 8° between probe and target). Participants were genotyped using TaqMan PCR. Group effects on accuracy (3 levels of load and 3 levels of difficulty) were marginal for rs914246 and significant for rs914245; the strongest effects of the latter were seen under high WM load with heterozygotes more accurate compared to both homozygote groups. The effect of microRNA silencing of reporter gene expression in mammalian cell lines and human primary neuron cultures are being used to validate these results and provide evidence on a mechanism of action for FTCD effects on WM. This mouse to human approach has the potential to increase knowledge of molecular mechanisms modulating WM--offering novel genetic predictors of WM performance and pathways for WM interventions.

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Poster

820. Cognition and Behavior: Human Working Memory

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Topic: F.01. Human Cognition and Behavior

Title: Features of neurodynamics of the human brain during a memory task depending on the level of emotional burnout

Authors: *S. TUKAEV[1], M. SYVASH[2];
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Abstract: Emotional burnout refers to a syndrome caused by chronic stress. The formation of emotional burnout may lead to persistent changes in cognitive activity and particularly in memory and attention. As the power of human EEG-spectrum components varies significantly under cognitive testing, the aim of our study was to investigate the dynamics of changes of EEG

parameters under a memory task depending on the severity of burnout. 42 healthy volunteers (students aged 18 to 24 years) participated in this study. EEG was registered over a period of 3 minutes during the rest state and 10 minutes during a verbal memory task. The spectral power density (SPD) of all frequencies from 0.2 to 35 Hz was estimated. The Mann-Witney criterion was carried out for the comparison of the independent data samples. The correlations were estimated using the Spearmen's coefficient correlation. In order to determine the stages of burnout we used the test “Syndrome of emotional burnout” (by Boyko), adapted for students. We observed variations in parameters of EEG during memorizing and retention phases depending on the intensity of the burnout. The intensity of the Exhaustion stage varied inversely with SPD in alpha3 (parietal and temporal regions), beta1 (parietal regions) and beta2 (parietal, right occipital and temporal regions) during the memorizing phase. The formation of the Exhaustion stage of burnout was accompanied by a decrease in alpha3 (parietal, left occipital and right temporal regions), beta1 (parietal, occipital and left temporal regions) and beta2 (parietal regions) during the retention phase. Our data indicate that short-term memory depends on the emotional state of subjects.

Disclosures: **S. Tukaev:** None. **M. Syvash:** None.

Poster

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Werner Reichardt Centre of Integrative Neuroscience (CIN)

Title: Facilitation of working memory training and transfer by prefrontal transcranial direct current stimulation (tDCS)

Authors: *C. PLEWNIA, P. RUF;
Univ. of Tuebingen, Tuebingen, Germany

Abstract: Background: Transcranial direct current stimulation (tDCS) applied to the dorsolateral prefrontal cortex (dlPFC) has been shown to modulate cognitive functions, particularly working memory (WM) performance. Since evidence regarding enhancement of WM-training by tDCS is less decisive, we set out to test efficacy, sustainability and transferability of a tDCS

augmentation of WM-training. As WM functions appear to be at least partially lateralized, we also addressed the interaction of task characteristics (spatial vs. verbal) and stimulation site (right vs. left). Methods: In two randomized, sham-controlled studies, 71 healthy, right-handed young adults were trained on an adaptive n-back task (Exp.I: spatial n-back: Exp.II: verbal n-back). Training was performed in six sessions comprising a baseline, three tDCS-enhanced trainings during one week, and two subsequent tDCS-free sessions (three days and three or nine months later). Anodal (1 mA, 20 min) or sham tDCS was applied to the left or right dlPFC parallel to the training. In sessions without tDCS (at baseline and the last two sessions), performance on a transfer-task (Exp.I: verbal 3-back: Exp.II: spatial 3-back) was tested. Results: Concurrent activation of the dlPFC by anodal tDCS improved learning of spatial and verbal n-back tasks when applied to the right and left dlPFC respectively. These effects were dependent on baseline performance. Most importantly, the tDCS-induced learning gains were found to be transferred to the untrained 3-back task and lasted for up to nine months. Conclusion: Our data clearly indicate that WM-training can be significantly enhanced by tDCS. The documented long-lasting, transferable, laterality- and task-specific effects of anodal tDCS point towards a behaviorally relevant and sustainable facilitation of underlying neuroplastic processes. This approach opens new perspectives for a targeted treatment of impaired executive functioning in various neuropsychiatric disorders.

Disclosures: C. Plewnia: None. **P. Ruf:** None.

Poster

820. Cognition and Behavior: Human Working Memory

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Topic: F.01. Human Cognition and Behavior

Title: Distinct effects of dopamine and subthalamic nucleus stimulation in associative learning and retention in Parkinson's disease

Authors: *J. VENTRE-DOMINEY[1], H. MOLLION[2], E. BROUSSOLLE[2];
[1]INSERM, Bron, France; [2]Neurol. Hosp., Lyon, France

Abstract: Parkinson's disease (PD) can affect cognitive functions including visual memory and learning which deficits can be at least partially compensated by dopamine medication or subthalamic nucleus stimulation. The effects of these PD therapies differ according to the learning processes involving the dorsal versus ventral part of the striatum. In this study we investigated and compared the outcomes of dopamine versus stimulation treatment in PD

patients ability to acquire and maintain over successive days their performance in visual working memory. PD patients performed conditional associative learning embedded in visual (spatial and non spatial) working memory tasks over two consecutive days either ON or OFF treatment. While PD patients were faster in memory tasks ON versus OFF stimulation independently of the day of testing, performance in medicated patients differed depending on the medication status during the task acquisition. PD patients who learnt the task ON medication the first day were able to maintain or even improve their memory performance both OFF and ON medication on the second day after consolidation. These effects were specific of dopamine mediation as it was observed in all patients with dopamine replacement whatever the age of the PD group. This enhancement in memory performance after having learnt under dopamine medication and not under STN stimulation was most significant in visuo-spatial working memory tasks suggesting that dopamine replacement in the depleted dorsal striatum is essential for retention and consolidation of learnt skill.

Disclosures: **J. Ventre-Dominey:** None. **H. Mollion:** None. **E. Broussolle:** None.

Poster

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Title: The neural correlates of working memory for temporal order information: An fMRI study

Authors: ***Y.-P. CHEN**[1], Y.-W. FANG[1,2], C.-P. LIN[3], O. J.-L. TZENG[1,3,4], H.-W. HUANG[5], C.-M. HUANG[1,4,6];
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Abstract: Working memory refers to the executive processes responsible for temporary storage and manipulation of various domains of information to guide goal-directed behavior. Much of the neuroimaging literature for working memory have focused on exploring neural mechanisms

of visuo-spatial working memory and little is known about the neural recruitment while processing temporal or sequential order information during working memory. In the present study, we employed functional magnetic resonance imaging (fMRI) to investigate the neural underpinnings of working memory for temporal order information and the effects of load on neural recruitment during memory encoding and maintenance. Participants were instructed to remember a sequence of the shapes with three level of working memory load (set size: 2-4) and responded to indicate whether or not the memory probe indicated the remembered order. Behavioral results showed slower reaction times and lower task accuracy during high load condition. A whole brain analysis revealed broad fronto-parietal activation during working memory encoding and maintenance for temporal order information, including left dorsolateral prefrontal cortex, middle frontal gyrus, and bilateral posterior parietal regions. Moreover, a significant load-related activation was observed in left inferior and superior parietal lobules, suggesting the capacity to modulate the neural resources in response to task demand. These findings are in line with findings from visuo-spatial working memory and provide additional evidence that posterior parietal region may play a functional role in modulation of working memory capacity for temporal order information.

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Poster

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ERC-2009-AdG-249425

ERC-2010-AdG-269716

Title: Neuroplasticity in the congenitally blind: Working memory training alters large-scale interactions of visual cortex

Authors: *J. M. RIMMELE[1], H. GUDI[2], G. NOLTE[1], B. RÖDER[2], A. K. ENGEL[1]; [1]Dept. of Neurophysiol. and Pathophysiology, Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany; [2]Biol. Psychology and Neuropsychology, Univ. of Hamburg, Hamburg, Germany

Abstract: In a highly connected brain, large-scale interactions are likely to play a pivotal role in neuroplasticity. In visually deprived humans, neuroplasticity might result in the integration of the unused visual cortex into existing functional networks. We tested this assumption in a working memory (WM) training paradigm. WM training was expected to strengthen the integration of visual cortex into WM networks in congenitally blind (CB) compared to sighted control (SC) participants. This approach allows investigating the functional relevance of large-scale connectivity of visual cortex by measuring connectivity changes induced by WM training, rather than pre-existing differences. CB and SC participants were matched in age, gender, education and handedness. CB and SC participants either underwent a WM training with voices (condition 1), a WM training with tactile stimuli (condition 2) or an active training-control task (condition 3). Prior to and after the training, MEG and behavioral responses were recorded while participants performed a 2-back auditory WM task. A comparison of pre-post training related connectivity changes (using imaginary coherence) between the CB and SC, revealed group differences in beta- and theta-band connectivity. Beta-band connectivity effects mainly comprised group differences between visual cortex and brain areas involved in WM processing (frontal, parietal, insular) and brain areas involved in auditory processing (superior temporal cortex). Beta-band connectivity increased only in the CB in the auditory trained (condition 1) compared to the training-control participants (condition 3). A follow-up analysis showed that the beta-band connectivity increase particularly involved brain areas of the right ventral visual stream (fusiform face area). In contrast, theta-band mediated group differences in connectivity were mainly observed between brain areas typically associated with WM processing (frontal, parietal, insular) and auditory processing (superior temporal cortex). Theta-band connectivity increased only in SC in the auditory trained (condition 1) compared to the training-control (condition 3) participants. Thus, WM training resulted in an integration of visual cortex into WM networks in the CB group. The specific involvement of the ventral visual stream during a voice recognition WM task suggests that the functional specificity of visual cortex is preserved after neuroplastic changes. The findings provide evidence for changes in large-scale interactions as a mechanism of neuroplasticity after visual deprivation.

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Poster

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Topic: F.01. Human Cognition and Behavior

Title: A master map of visual-spatial working memory: meta-analysis of neuroimaging data

Authors: *Y.-F. LIANG[1], C.-M. HUANG[1,2,3];
[1]Inst. of Biomed. Engin., Natl. Chiao-Tung University,, Hsinchu, Taiwan; [2]Inst. of Mol. Med. and Bioengineering, [3]Dept. of Biol. Sci. and Technol., Natl. Chiao-Tung Univ., Hsinchu, Taiwan

Abstract: Neurophysiological studies in monkey and neuroimaging studies in human have suggested a functional division between two neural systems for supporting different aspects of visual information processing, with what neural system (ventral pathway) essential for object identification and where neural system (dorsal pathway) critical for spatial guidance. The brain areas devoted to what and where processing may communicate extensively when processing visuo-spatial information that requires temporary storage and active manipulation. Here, we investigate the effects of stimulus content on the ventral and dorsal neural pathways during visual-spatial working memory (VSWM) with a meta-analysis approach, using activation likelihood estimation (ALE) to compute statistically significant concordance with published coordinates across independent studies. Studies were categorized into the specific nature of visual stimuli: object, location, binding and task load. Meta-analytic results demonstrated that retrieval of items was associated with the activation in left middle frontal gyrus, left inferior parietal lobule and left precentral gyrus, whereas retrieval of location was related to the activation in bilateral superior parietal lobule, bilateral middle frontal gyrus and right cingulate gyrus. In addition, bilateral middle frontal gyrus, right superior frontal gyrus, bilateral precuneus and left insula are strongly associated with binding effects. Moreover, left middle frontal gyrus and right superior parietal lobule showed increased activity with higher level of memory load. These results provide a quantitative meta-analytic evidence and general view of how VSWM operates within the ventral and dorsal neural pathways.

Disclosures: Y. Liang: None. **C. Huang:** None.

Poster

820. Cognition and Behavior: Human Working Memory

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 820.19/BB45

Topic: F.01. Human Cognition and Behavior

Title: Distractor-resistant working memory representations revealed with MEG

Authors: K. KOMEK KIRLI, *K. K. SREENIVASAN;
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Abstract: Visual working memory (WM) allows us to maintain high-fidelity visual representations over brief intervals. The nature of these representations is a topic of considerable debate. An essential feature of WM is the ability for maintained visual representations to persist despite incoming visual input. Thus, a complete account of how WM is instantiated requires an understanding of how these representations survive distraction. To investigate how visual WM representations survive distraction, we recorded magnetoencephalographic (MEG) data from participants as they performed a WM task for orientation. On each trial, participants were presented with a lateralized oriented sample grating. They were instructed to remember the sample orientation over a retention interval. During this retention interval, distractor grating with a different orientation than the sample was presented at the same location as the previous sample; participants were instructed to ignore the distractor. At the end of the interval, participants reported the maintained sample orientation. We employed a forward encoding analysis of the MEG data in order to reconstruct the orientation of the sample grating (1) during the presentation of the sample, (2) during the retention interval prior to the onset of the distractor, and (3) during the retention interval following the offset of the distractor. The forward encoding analysis maps the MEG frequency data across sensors to putative orientation channels tuned to different orientations. We used this procedure to identify this mapping between sensor data and orientation channels and used these estimates to calculate the response of these orientation channels in independent data derived from our three time points of interest. Channel responses were then used to reconstruct the orientation at our three time points of interest. We separately analyzed sensors contra- and ipsilateral to the sample and distractor gratings. We were able to reconstruct the sample orientation using MEG data across multiple frequency bands - most prominently in the beta (15-30 Hz) range. Reconstruction was successful at all three time points in ipsilateral and contralateral sensors. Estimates of orientation reconstructed from contralateral sensors exhibited a shift in the direction of the distractor orientation following distractor presentation. Critically, orientation estimates reconstructed from ipsilateral sensors were unaffected by the distractor. Our results suggest that recruitment of the ipsilateral hemisphere may be a potential mechanism by which WM representations are protected from corruption by irrelevant visual input.

Disclosures: K. Komek Kirli: None. **K.K. Sreenivasan:** None.

Poster

820. Cognition and Behavior: Human Working Memory

Location: Hall A

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Program#/Poster#: 820.20/BB46

Topic: F.01. Human Cognition and Behavior

Title: Moving dipoles analysis and it's implication during stroop task : MEG Study

Authors: *S.-J. HWANG[1,2,3], W. CHANG[1], B. KIM[4], J. CHANG[1,2];
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Abstract: BackGround & Purpose : Magnetoencephalography is a functional neuroimaging technique for mapping brain activity by recording magnetic fields produced by electrical When the name and color are matched, we called 'congruent', is not 'incongruent' currents occurring naturally in the brain. MEG is a very effective way of spatial and temporal analysis of the number of nerve activity in the brain. While performing the cognitive task that we want to find area of the brain is activated and the reaction by the analysis of neural activity. Stroop; working memory task is a cognitive task that we will track to the movement of the dipole generated during the tasks Methods : Stroop effect is a demonstration of interference in the reaction time of a task. When the name of a color (e.g., "blue", "green", or "red") is printed in a color not denoted by the name (e.g., the word "red" printed in blue ink instead of red ink), naming the color of the word takes longer and is more prone to errors than when the color of the ink matches the name of the color. When the name and color are matched we called 'congruent', aren't matched 'incongruent'. 6 people were included in the analysis. Recording the MEG data during the stroop task and make the ERP and find the dipoles. Results : In the behavior response, Congruent and incongruent reaction time showed a difference. Congruent reaction time is more faster than incongruent. Percentage of correct answers in the case of some falling trend seems incongruent. But not the trend seems to be common from all subjects. The dipole analysis in the period of stroop task, dipole be formed in the same area of brain. And also we can find the difference of dipole strength between congruent and incongruent. The difference of reaction time between 'congruent' and 'incongruent' causes delay neuronal activity process in a particular parts of the brain. It will be frontal of the brain. So we can find dipole delaying of the brain during the stroop task.

Disclosures: **S. Hwang:** None. **W. Chang:** None. **B. Kim:** None. **J. Chang:** None.

Poster

820. Cognition and Behavior: Human Working Memory

Location: Hall A

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Program#/Poster#: 820.21/BB47

Topic: F.01. Human Cognition and Behavior

Support: Neuronetrix COGNISION System Grant Program

Title: Energy drinks effects on cognitive performance as measured by auditory event-related potentials and quantitative EEG in college students

Authors: C. WALLACE, *N. R. CAPRILES;
Kentucky State Univ., Frankfort, KY

Abstract: Popularity of energy drinks (EDs) has dramatically increased among college students in recent years. This increase may be associated to beneficial effects, such as improved alertness and concentration that EDs claim to provide. Event-related potentials (ERP) and quantitative EEG (qEEG) are cutting edge cognitive measures that allow real-time recordings of cortical brain activity, and were used to investigate the pro cognitive effects of EDs. The present study investigated: 1) pattern of consumption of EDs in college students; 2) college student's perception of ED effects; 3) ED effects on ERP and qEEG measures; and 4) contribution of sugars to the cognitive effects associated to ED. Thirty college students participated in this study. Subjects were screened for their pattern of consumption of caffeinated beverages by answering a forty questions survey. Subsequently, equal numbers of participants were randomly assigned to one of three experimental conditions: ED (regular ingredients), ED (sugar free), or placebo. The testing protocol consisted of two sessions where ERP evoked by auditory stimuli and 3-min of resting EEG were recorded: pretest (baseline) and test (60-min after treatment). Preliminary results show that the classic ED improved ERP measures of memory, focal attention and executive function. Reaction time and accuracy associated with the target detection task of the ERP test were also affected. Finally classic ED significantly increased peak alpha frequency, a qEEG measure that correlates with performance in cognitive tasks and is inversely related to aging. Analysis of the contribution of sugars on the effects of ED is underway.

Disclosures: C. Wallace: None. **N.R. Capriles:** None.

Poster

820. Cognition and Behavior: Human Working Memory

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 820.22/BB48

Topic: F.01. Human Cognition and Behavior

Title: Dual task of working memory in action video game players: prefrontal eeg correlation

Authors: *J. C. LLAMAS, M. L. ALMANZA-SEPÚLVEDA, M. HERNÁNDEZ-GONZÁLEZ, M. A. GUEVARA;
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Abstract: Constant practice in action video games has been shown to improve different cognitive process such as working memory. Action video games require the optimization of executive control skills to coordinate two different tasks. Considering that prefrontal cortex, specially frontopolar and dorsolateral areas are closely related to the functioning of working memory and dual tasks performance, the aim of this study was to characterize prefrontal EEG correlation in action video game players (AVGPs) during the performance of a working memory dual task. The EEG from frontopolar (F1-F2) and prefrontal (F3-F4) areas was recorded in young men of the AVGPs and of the subjects of a control group conformed by non-video game players (NVGPs) under four conditions: 1) basal eyes open, 2) N-back condition (1-back), 3) Corsi Block-Tapping task in forward condition and 4) during dual task of both conditions. Significant differences were found between groups in the performance of the dual task, AVGPs retained a higher maximum number of items in memory and had a higher number of correct answers than NVGPs. Only the AVGPs showed a higher left and right intrahemispheric frontopolar and prefrontal correlation (F1-F3) (F2-F4) in the beta 2 (20-30 Hz) and gamma (31-50 Hz) band as well as a higher interhemispheric EEG correlation (F1-F2) during dual task performing. These data shown that the experience in action video games change the coupling degree between prefrontal cortex, especially in frontopolar and dorsolateral prefrontal areas, which play a main role in working memory and dual task performance. It is probable that this higher degree of coupling in prefrontal cortices could represent a characteristic pattern of brain functionality in AVGPs when they process, retrieve, manipulate and optimize information during the performance of dual task with a working memory component.

Disclosures: J.C. Llamas: None. **M.L. Almanza-Sepúlveda:** None. **M. Hernández-González:** None. **M.A. Guevara:** None.

Poster

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Topic: F.01. Human Cognition and Behavior

Support: Dartmouth iQBS/SYNERGY

Title: Comparison of conventional electroencephalography (EEG) and inexpensive wireless EEG systems during a working memory task

Authors: *G. NOTARO[1], J. M. QIU[1], P. GIACOMETTI[1], J. D. SARGENT[3], T. F. HEATHERTON[2], D. GILBERT-DIAMOND[4], S. DIAMOND[1];
[1]Engin., [2]Psychological and Brain Sci., Dartmouth Col., Hanover, NH; [3]Pediatrics, [4]Epidemiology, Geisel Sch. of Med. at Dartmouth, Hanover, NH

Abstract: In recent years, the emergence of inexpensive electroencephalography (EEG) devices has broadened the potential scope of applications for neurophysiological study. However, before inexpensive, wireless EEG devices can be used reliably in neuroscience research, the data quality of each device should be assessed through comparison to research-grade EEG systems. Consequently, we compared a conventional wired ANT Neuro EEG system to the low-cost, wireless OpenBCI EEG system. The OpenBCI system was selected over other low-cost EEG systems due to its greater flexibility in electrode placement. All electrodes were positioned using a rubber head cap, designed by our lab previously, to secure the EEG electrodes according to the 10-20 electrode montage. Electrodes from the OpenBCI system were secured at eight coincident positions with the electrodes for the ANT system [F3, F4, C3, C4, P3, P4, O1, O2] using matching reference and ground positions. Since preliminary data suggest no interference between the ANT and OpenBCI systems during simultaneous data collection, subjects were recruited for experimental testing. A letter-based N-back working memory task was selected for our study due to its frequent use in neuroscience research. An N of two was selected for moderate difficulty and maximal task attention, and was implemented using PsychoPy. Both upper- and lower-case letters [b, B, d, D, g, G, p, P, t, T, v, V] were selected to reduce visual and phonological strategies during the task. During simultaneous EEG recording, letters were presented in sequence to the subject at the center of the screen, following an initial fixation period to collect baseline data. All data were processed offline using Matlab. Signals recorded by the ANT Neuro and OpenBCI EEG systems were compared during baseline fixation and task conditions using both time and frequency domain analyses. Signal-to-noise analyses revealed comparable performance below 40 Hz but larger high-frequency noise by a factor of 10 in the OpenBCI system. The overall correlation of EEG waveforms between the two systems in the 4 to 40 Hz range was low ($R2 = 0.05$), suggesting that the two systems are independently noise dominated. Coherence analysis was also performed between signals from the two devices to examine the frequency dependence of the correlations. The magnitude squared coherence peaked at 0.25 in the alpha band of the occipital electrodes. Performing these comparative tests on inexpensive EEG devices is critical in order to understand signal quality issues for designing future studies. This foundational work will enable future studies by our group on the neurophysiology of children in naturalistic environments.

Disclosures: **G. Notaro:** None. **J.M. Qiu:** None. **P. Giacometti:** None. **J.D. Sargent:** None. **T.F. Heatherton:** None. **D. Gilbert-Diamond:** None. **S. Diamond:** None.

Poster

820. Cognition and Behavior: Human Working Memory

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Program#/Poster#: 820.24/BB50

Topic: F.01. Human Cognition and Behavior

Title: Intracranial oscillatory activity in patients performing an object-in-place scene memory task

Authors: *J. J. YOUNG[1], A. FAZL[1], L. V. MARCUSE[1], M. C. FIELDS[1], M. G. BAXTER[2]; [1]Dept. of Neurol., [2]Dept. of Neurosci., Icahn Sch. of Med. At Mount Sinai, New York, NY

Abstract: Patients with medically refractory epilepsy are sometimes considered for surgical intervention, and an important pre-operative procedure in the treatment of these patients is an intracranial electroencephalogram (EEG). Patients undergoing this procedure also provide a valuable resource for understanding how oscillatory activity supports memory and decision making in humans. Subjects undergoing intracranial EEG underwent cognitive testing using an object-in-place scene memory test, a task where the subject was required to recognize sets of correct targets on a colored background. Their performance on this task was compared to the oscillatory activity in their brain. Spectral power across frequencies, comodulation of different frequencies, and coherence in oscillation between brain regions were compared to determine the types of activity most predictive of good performance.

Disclosures: **J.J. Young:** None. **A. Fazl:** None. **L.V. Marcuse:** None. **M.C. Fields:** None. **M.G. Baxter:** None.

Poster

820. Cognition and Behavior: Human Working Memory

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 820.25/BB51

Topic: F.01. Human Cognition and Behavior

Title: Title:Study of working memory capacity by cerebral blood flow changes : study using reading span test

Authors: *K. TAKI, T. HIROYASU;
Doshisha Univ., Kyotanabe, Kyoto, Japan

Abstract: [Purpose]The capacity of working memory (WM) is different depending on the person. Up to now, evaluation method of WM capacity of the brain function measurement has not been established. Therefore, we examined the relationship between performance of reading span test (RST) and brain regions involved in WM. [Method]Cerebral blood flows changes in subjects 20 people during RST were measured. Whole brain (116 measurement channels) was measured as the measurement range by near infrared spectroscopy. In order to analyze, subjects were classified to high performance group and the low performance group by a score of RST. Then hemodynamic model was created by convolution of hemodynamic response function (HRF) and rectangular function that based on the experimental design. In consideration of individual differences, parameters of HRF were determined by the optimization in order to match as much as possible the measurement data and hemodynamic model. Based on dynamic time warping (DTW) distance between the measurement data and the hemodynamic response model created, difference in brain activity between high performance group and the low performance group was examined. [Results]In the performances of top six people and the performance of subordinate six people, there was a major difference by t-test ($p < .01$). Differences in brain activity between these groups were examined. We consider that the measurement channel is not active if DTW distance between the hemodynamic response model created and the measurement data is large. DTW distance between the two groups measurement channel was compared by t-test. When the p-value is low, the difference between the two groups of DTW distance is greater. Through the result of the examination, a significant difference was found in DTW distance between the prefrontal dorsolateral, Wernicke's area in left hemisphere and motor cortex. Thus, it is found that regions involved in WM performance of the top person are more active than the low performance person. It is suggested that these relationships regions brings a difference in performance. [Discussion]The comparison result high performance group DTW distance between the hemodynamic model and the measured data showed more active than regions of low performance group. Comparing peak arrival time of blood flow between these areas, peak of the prefrontal dorsolateral (central executive) is earlier than the peak of Wernicke's area. This result indicates that activity of Wernicke’s area is weak because of inadequate control of the central executive. [Conclusion]The present study showed that the high performance group has a high ability to control by the central executive to RST.

Disclosures: **K. Taki:** None. **T. Hiroyasu:** None.

Poster

820. Cognition and Behavior: Human Working Memory

Location: Hall A

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Program#/Poster#: 820.26/BB52

Topic: F.01. Human Cognition and Behavior

Title: The contralateral delay measures spatial working memory and is altered with encoding strategy

Authors: *L. RABBITT, M. S. PETERSON, C. G. MCDONALD;
George Mason Univ., Fairfax, VA

Abstract: Spatial working memory capacity is limited in the number of items that can be maintained over time. However, similar to verbal working memory, previous research has demonstrated that spatial working memory (SWM) can be improved when stimuli are organized into familiar patterns. The current study examined the neural correlates of SWM, specifically if SWM could be measured with the contralateral delay activity (CDA), an event-related potential known to index visual working memory. Additionally, the study investigated whether or not task instruction would alter the amplitude of the CDA. In the current study, participants performed a SWM change detection task that required participants to remember the locations of colored squares on one side of the screen, indicated by a cue prior to the beginning of the trial. Participants were given one of two instruction types: to remember the location of the squares, or to remember the constellation of the squares. Results of this study demonstrate that the CDA is able to index SWM capacity; as the number of items in SWM increases, the amplitude of the CDA increases. The manipulation of task instruction also had an effect on the amplitude of the CDA. Examining the amplitude change from two to four items, the spatial instruction CDA increased for both high and low working memory individuals. In contrast, for the constellation CDA, as individuals' capacity increased, their CDA amplitude difference decreased. These results indicate the CDA can measure SWM and how encoding strategy affects the electrophysiological measures of SWM.

Disclosures: L. Rabbitt: None. **M.S. Peterson:** None. **C.G. McDonald:** None.

Poster

820. Cognition and Behavior: Human Working Memory

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Program#/Poster#: 820.27/BB53

Topic: F.01. Human Cognition and Behavior

Title: Neural correlates of signal detection parameters for working memory

Authors: *T. KARPOUZIAN, H. BREITER, J. REILLY;
Psychiatry and Behavioral Sci., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: Objective: Working memory (WM) involves the temporary mental maintenance and manipulation of information to support higher order cognitive operations. The neural circuitry supporting WM is well established; however, it is not clear which regions underlie the ability to maintain signal from noise as characterized by signal detection theory. To evaluate the neural basis of these WM component processes, we conducted an event-related fMRI study in which we parametrically manipulated the amount of information (i.e., load) held in WM and characterized performance according to the signal detection parameters of d', the ability to maintain segregation of signal and noise distributions, and B, a measure of response bias in allowing false alarms. Methods: Twenty-one healthy adults completed a WM task while undergoing fMRI. Subjects were briefly presented with a stimulus array consisting of 3, 5, or 7 items. After a variable delay period, a probe item was presented and the subject decided if it appeared in the same location as one of the array items. d', B, and response time, as a measure of efficiency of response selection, were calculated for each load level. fMRI analyses identified regions of activation during correctly performed trials, and how activation changed over increasing WM load. Results: A RM-ANOVA revealed that WM accuracy (d') parametrically declined with increasing load ($F_{(2, 38)}$ =18.69, $p < .001$), individuals were more conservative in allowing False Alarms (B) as load increased ($F_{(2, 38)}$ =9.23, p<.001), and response time increased as load increased, ($F_{(2, 38)}$ =22.77, $p < .001$). fMRI analyses demonstrated activation during correctly performed trials in the superior parietal lobule, insula, dorsolateral prefrontal cortex, anterior cingulate cortex, and thalamus. A RM-ANOVA revealed a significant increase in percent signal change across WM load in the parietal lobe ($F_{(2, 38)}$=4.692, p=.015). Correlation analysis revealed a significant correlation between change across WM load in d' and activation in the insula and temporal lobe. Discussion: An increase in WM capacity demands lead to a diminished ability to separate signal from noise, a greater bias towards becoming more conservative in allowing false alarms, and longer response times. This increase in WM is associated with an increase in BOLD activation across the WM circuit to correctly maintain information, particularly in the parietal lobe. The ability to separate signal from noise with increasing WM load was associated with increased activation in the temporal lobe and the insula. These findings suggest differential roles within the WM functional circuitry to support component processes of WM ability.

Disclosures: T. Karpouzian: None. **H. Breiter:** None. **J. Reilly:** None.

Poster

820. Cognition and Behavior: Human Working Memory

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Topic: F.01. Human Cognition and Behavior

Support: DFG BL 931/3-1

LOEWE Neuronal Coordination Research Focus Frankfurt (NeFF)

Title: A whole report approach improves assessment of item precision in visual working memory

Authors: *B. PETERS[1], B. RAHM[2], C. BARNES[1], J. KAISER[1], C. BLEDOWSKI[1]; [1]Goethe-University, Frankfurt Am Main, Germany; [2]Univ. Med. Ctr., Mainz, Germany

Abstract: Visual working memory (vWM) is highly capacity limited. Both the nature of its limitations and their neuronal origins remain highly debated. The effect of capacity limitation is typically assessed by asking participants to reproduce a single item of those held in vWM and examining the precision of this report dependent on memory set size. This procedure, however, does not yield specific information about within-trial variations of the precision of individual memory representations, which may be used to evaluate competing models of vWM capacity. We implemented a whole-report vWM task asking subjects to successively report each of the previously encoded items in a continuous recall format. We thus obtained estimates of individual item-precision data and were better able to separate them from performance fluctuations across trials. A series of behavioral experiments was conducted, providing a detailed characterization of the sequence of recall precisions. We found that subjects were able to recall the orientation of visual gratings above chance even at set size six and that the total amount of retrieved information was independent of whether the recall sequence was defined by the experimenter or chosen by the participant. Precision, however, varied systematically with recall order and set size. The first item in a recall sequence was reported with the highest precision. This was comparable to the typical situation where only one item has to be reported. Precision was increasingly diminished for subsequently reported items, whereby the reduction in precision from the first to the second recalled item was much steeper than for further items. This special status of the first recalled item was eliminated when subjects attended interfering visual stimuli before recall, but not by a longer memory delay. These results show that the whole report procedure is feasible and yields information about within-trial variations of item precision that is not available from standard single report paradigms. By accounting for the interference of the whole-report sequence, we were better able to separate the distribution of within-trial information from across trial performance fluctuations. This in turn improves evaluation of

competing models of vWM capacity that make different predictions regarding within-trial correlations of item precisions. Item-wise precision information can be related to concurrently recorded brain activity using, e.g., magnetoencephalography.

Disclosures: B. Peters: None. **B. Rahm:** None. **C. Barnes:** None. **J. Kaiser:** None. **C. Bledowski:** None.

Poster

820. Cognition and Behavior: Human Working Memory

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Topic: F.01. Human Cognition and Behavior

Support: NIMH Grant MH63901

Title: Distractor resistance for precise visual working memory

Authors: *E. S. LORENC[1], K. K. SREENIVASAN[2], D. E. NEE[1], A. R. E. VANDENBROUCKE[1], M. D'ESPOSITO[1];
[1]Neurosci., UC Berkeley, Berkeley, CA; [2]New York Univ. Abu Dhabi, Abu Dhabi, United Arab Emirates

Abstract: Visual working memory (VWM) is essential for our ability to maintain information about stimuli that are no longer in view. In daily life, we rely on this skill to maintain relevant information about objects in our environment and manipulate that information in the service of goal-directed behaviors. Previous research has suggested that both the prefrontal cortex (D'Esposito et al., 1995, 1996) and stimulus-selective primary sensory cortices (Harrison & Tong, 2009) support visual working memory maintenance. So-called "sensory recruitment" models (D'Esposito, 2007; Postle, 2006) posit that the same brain regions responsible for primary stimulus processing continue to maintain visual information over a short delay. However, these models do not explain how the brain maintains VWM representations when subsequent visual input is processed. Therefore, this study investigates whether VWM distractor-resistance is supported by distributed cortical representations outside those areas particularly involved in initial perception. In this experiment, participants performed a VWM task in which they had to remember the precise orientation of a lateralized sine wave grating over a long delay period (~20s) and report their memory contents via a method-of-adjustment procedure. On 2/3 of trials, a distractor grating appeared midway through the trial in the same spatial location as the initial memory cue, which participants were instructed to ignore. Functional magnetic resonance

imaging (fMRI) data was collected during this task. A forward encoding modeling approach (Brouwer & Heeger, 2011; Ester et al., 2013) was used to iteratively reconstruct tuning functions reflecting the accuracy and precision of orientation information held in working memory throughout each trial. Reliable stimulus perception-related orientation tuning curves were recovered in the contralateral, but not ipsilateral, early visual areas (V1-V2). However, the memory representations spread to include the ipsilateral early visual areas over the course of the first delay interval. After distractor presentation, reliable tuning functions remained in a subset of early visual areas in both hemispheres, despite the new visual input. These results converge with earlier fMRI evidence that VWM representations do not exhibit the same level of retinotopic specificity as visual perception (Ester et al., 2009), and suggest that this loss of spatial specificity may support the continued maintenance of precise visual details through subsequent visual input.

Disclosures: **E.S. Lorenc:** None. **K.K. Sreenivasan:** None. **D.E. Nee:** None. **A.R.E. Vandenbroucke:** None. **M. D'Esposito:** None.

Poster

820. Cognition and Behavior: Human Working Memory

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Topic: F.01. Human Cognition and Behavior

Support: Marie Curie FP7-PEOPLE-2013-IOF 624380

Title: The neural correlates of unattended working memory representations

Authors: *A. R. VANDENBROUCKE[1], E. S. LORENC[1], D. E. NEE[1], F. P. DE LANGE[2], M. D'ESPOSITO[1];
[1]Psychology, Univ. of California, Berkeley, Berkeley, CA; [2]Donders Inst. for Brain, Cognition and Behavior, Nijmegen, Netherlands

Abstract: In daily life, humans use visual working memory to remember and perform cognitive operations on visual objects in their environment. Over the last few decades, research has shown that both prefrontal (D'Esposito et al., 1995, 1996) and visual cortex (Harrison & Tong, 2009; Serences et al., 2009) support visual working memory maintenance. Whereas prefrontal areas are mainly associated with task set and goals associated with working memory (Nee & Brown, 2013), visual cortex is thought to be involved in the actual storage of memory items (Riggall & Postle, 2012). However, paradigms used to investigate storage of visual working memory typically require the maintenance of a single item in the absence of distraction. This does not

seem to mimic the demands that are usually placed on visual working memory systems. The current study examines which cortical regions support the concurrent maintenance of two items, especially when participants switch attention between the two. In this study we recorded neural activity using fMRI while participants remembered either one or two orientation gratings. After simultaneous presentation of two lateralized gratings, a cue (100% valid) was presented that indicated which item would first be probed (left or right), and whether the second item should be maintained in working memory for later recall (green cue) or not (red cue). After a 10-second delay period, participants performed a change detection task on the first cued item. Then, either a new trial started or the second item was cued, and after another 10-second delay period participants performed a change detection task on the second cued item. To investigate whether the attended (first cued) and unattended (second cued) memory item were neurally represented in visual cortex, we used a forward encoding modeling approach (Brouwer & Heeger, 2011; Ester et al., 2013). In this approach, the orientation selectivity of each voxel is modeled using hypothetical channels with an idealized tuning curve. After training the model on a subset of the data, the remaining data can be used to reconstruct the remembered stimulus orientation. Preliminary results show that in the first memory delay, we are able to reconstruct the representation of the two stimuli from activity in corresponding retinotopic locations in early visual cortex. However, reconstruction from the second memory delay is not as pronounced. Current analyses focus on determining if the memory representations can be detected in cortical areas outside the specific retinotopic regions involved in initial stimulus perception, including other areas of visual cortex, as well as the intra-parietal sulcus and prefrontal cortex.

Disclosures: **A.R. Vandenbroucke:** None. **E.S. Lorenc:** None. **D.E. Nee:** None. **F.P. de Lange:** None. **M. D'Esposito:** None.

Poster

821. Individual Differences

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Program#/Poster#: 821.01/BB57

Topic: F.01. Human Cognition and Behavior

Title: Relationship between large-scale cortical networks estimated by structural covariance and resting-state functional connectivity MRI

Authors: *E. DUPRE, N. SPRENG;
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Abstract: Large-scale distributed cortical networks are a central feature of human brain organization. These large-scale networks can be observed by examining the low-frequency oscillations of fMRI blood-oxygen level dependent (BOLD) signal. Additionally, structural covariance networks can be observed by examining covariation in interindividual differences in regional brain structure. In this study, we sought to examine the convergence of these network methods. Using structural T1 images and resting-state BOLD timeseries data from the Human Connectome Project, we investigated structural covariance and resting-state functional networks across the motor, visual, dorsal attention, salience, frontoparietal control, and default networks. For all analyses, networks were extracted using four literature-defined seeds. For structural covariance networks, Partial Least Squares, a multivariate analytical technique, was used to derive structural covariance networks. This approach provides individual subject values, 'brain scores', representing a global estimate for the structural integrity of the system identified at the group level. For resting-state analyses, time courses were extracted from each network seeds, correlated, and averaged across correlations to derive a network level value. In associating these two measures, we found that structural and functional results correlated in only a subset of the networks. The most robust association was with the frontoparietal control network. Structural covariance measures were more reliable predictors of self-report behavioral measures. Structural frontoparietal control network scores were associated with Openness, a big five personality factor closely associated with intelligence. Overall, there is not a strict equivalence between resting state functional connectivity networks and structural covariance networks, potentially reflecting the differential timescales exhibited at each level of organization. Greater association with behavior may reflect the longer time scales at which trait-level behaviors are present.

Disclosures: E. Dupre: None. **N. Spreng:** None.

Poster

821. Individual Differences

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 821.02/BB58

Topic: F.01. Human Cognition and Behavior

Support: ARC Award DE140101375

Title: Function follows form: Relating brain anatomy and physiology to cognition and psychology

Authors: *C. KERR[1,2,3], R. M. STUART[4], K. F. TURNER[5];
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State Univ. of New York Downstate Med. Ctr., Brooklyn, NY; [3]Brain Dynamics Ctr., Westmead Hosp., Sydney, Australia; [4]Dept. of Mathematical Sci., Univ. of Copenhagen, Copenhagen, Denmark; [5]Dept. of Mathematics, Univ. of Chicago, Chicago, IL

Abstract: For over two centuries, scientists have yearned to explain differences in cognition and psychology through differences in anatomy and physiology -- from the galling pseudoscience of phrenology to more sober techniques such as diffusion tensor imaging. Modern studies have typically focused on the existence of specific correlations, such as between gray matter volume and performance on a given cognitive task. However, recent improvements in data recording and storage, coupled with advances in data mining and other statistical techniques, have enabled the creation and analysis of large databases, allowing more general principles to be extracted. In this study, we analyzed data from 1498 subjects drawn from the Brain Resource International Database (www.brainnet.net), the largest available library of standarized, cross-modal human brain measures. Almost 300 separate measures were available for each subject, including demography (age, sex, etc.), mood (anxiety, depression, etc.), personality (extroversion, openness, etc.), cognition (verbal memory, reaction time, maze completion, etc.), electroencephalography (EEG; eyes-open and closed power spectra), and structural magnetic resonance imaging (MRI; gray and white matter volumes). We answer several of the most basic -- and most important -- questions that can be addressed with this dataset: How much of the variation in cognitive and psychological measures can be explained by variation in brain anatomy and physiology? Which of these measures have the strongest explanatory power? How do the measures covary with age? A generalized linear model (GLM) was able to explain a significant fraction of the total variation in the cognitive, mood, and personality measures, with much of the explanatory power attributable to the EEG and MRI variables. On average, measures within a given modality tended to be strongly correlated with each other (e.g., gray matter volumes in different parts of the brain). There were statistically significant age effects for task performance, EEG power, and gray and white matter volumes, including some striking parallels between very young and very old subjects. In summary, to our knowledge, this work presents the most comprehensive picture to date of the interrelations between anatomical, physiological, cognitive, and psychological measures of the human brain.

Disclosures: **C. Kerr:** None. **R.M. Stuart:** None. **K.F. Turner:** None.

Poster

821. Individual Differences

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 821.03/BB59

Topic: F.01. Human Cognition and Behavior

Support: Institute for Collaborative Biotechnologies grant W911NF-09-D-0001

Title: The relationship between individual difference factors and brain activity varies across tasks and brain regions

Authors: *B. O. TURNER, M. B. MILLER;
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Abstract: Between-participant variability in brain activity is frequently treated as a nuisance to be minimized so that the "true" activity can be revealed. However, a long line of research has demonstrated that, in many cases, group-level activity maps bear little resemblance to the map of any individual. Moreover, by comparing brain activity within and between participants performing multiple tasks, it is clear that a substantial proportion of the brain activity observed for any individual is due to intrinsic, rather than task-related, factors (Miller et al., 2009). Accordingly, this variability in activity between participants has been shown to be related to a variety of individual difference factors, including demographics, anatomy, task strategy, and performance (Miller et al., 2012). Here, in a large-scale (N=95) study of recognition memory, we extend this line of research in two ways. First, the number and variety of individual difference factors measured for each individual is greatly expanded to include well over 100 measures. Second, in addition to whole-brain activity patterns, we explore between-participant similarity at a regional level. We expect that multiple realizability may result in some regions whose activity is highly influenced by these individual difference factors; in other regions, activity may be conserved across individuals. In each region, we computed between-participant similarity in the regional pattern of brain activity for each pair of participants. These similarity scores were then entered into a hierarchical regression, with groups of variables from domains including brain measures, cognitive factors, demographics, state of mind, mental health, performance, and personality, operationalized as between-participant similarity on each measure. Finally, we determined the unique portion of variance accounted for by each group of variables in each region. Our results demonstrate that, as predicted, regions vary markedly in terms of what types of variables influence brain activity. Of particular interest is how these relationships interact with the memory task. For example, in a condition putatively requiring a high degree of cognitive control, performance-related factors had the most explanatory power, while in a separate condition with lower cognitive demands, several other groups of variables including personality and state of mind surpassed performance-related factors. These results speak to the need to interpret neuroimaging results through the lens of the individuals being studied. This research was supported by the Institute for Collaborative Biotechnologies under grant W911NF-09-D-0001.

Disclosures: **B.O. Turner:** None. **M.B. Miller:** None.

Poster

821. Individual Differences

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 821.04/BB60

Topic: F.01. Human Cognition and Behavior

Support: NIDA Grant R01DA031579

NIDA Grant R01DA033369

NSF Graduate Research Fellowship

Title: A polygenic risk profile for schizophrenia is associated with intrinsic connectivity of the dorsolateral prefrontal cortex and general cognitive ability

Authors: *J. MILLER[1], M. SCULT[2], Q. CHEN[3], D. WEINBERGER[3], A. HARIRI[2]; [2]Psychology & Neurosci., [1]Duke Univ., Durham, NC; [3]Lieber Inst. for Brain Develop., Baltimore, MD

Abstract: Using data from the ongoing Duke Neurogenetics Study, we tested for associations between a recently constructed schizophrenia polygenic risk score (Schizophrenia Working Group of the Psychiatric Genomics Consortium. Nature. 2014 Jul 24;511 (7510):421-7) and variability in the intrinsic connectivity of the dorsolateral prefrontal cortex. We further explored associations between risk scores and general cognitive ability. Resting-state fMRI data, polygenic risk scores, and a factor-derived measure of general cognitive ability were available for 332 non-Hispanic Caucasian young adults. Analyses revealed significant modulatory effects of the polygenic risk score on dorsolateral prefrontal cortex intrinsic connectivity and general cognitive ability. Furthermore, effects of the polygenic risk score on cognitive ability were partially mediated by variability in prefrontal connectivity. We discuss these findings with regard to pathophysiologic mechanisms of risk in schizophrenia as well as the general neurogenetic architecture of general cognitive ability.

Disclosures: J. Miller: None. **M. Scult:** None. **Q. Chen:** None. **D. Weinberger:** None. **A. Hariri:** None.

Poster

821. Individual Differences

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 821.05/BB61

Topic: F.01. Human Cognition and Behavior

Title: Verbal ability and inner speech qualities

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Abstract: Inner speech plays a role in the rehearsal process of verbal working memory (Baddeley, 1992), planning (Lidstone, et al., 2010), and self-awareness (Morin & Michaud, 2007). We previously reported correlations between aspects of inner speech and schizotypal personality traits. However there has been little work investigating relationships between qualities of inner speech and overall verbal ability or with other endophenotypes of other neurological disorders. Participants (n = 110; 74.5% female) were assessed for inner speech qualities, schizotypal personality traits, empathizing and systemizing; SAT scores were also obtained. Individuals with higher verbal ability, as measured by SAT verbal scores, had more dialogic inner speech (r (74) = .236 p = .040) and less condensed verbal speech (r (74) = -.269 p = .019). Males with higher math ability as measured by SAT math score also had less condensed inner speech (r (20) = -.477 p = .025). Additionally, individuals that scored higher on systemizing had more evaluative/motivational inner speech (r (110) = .270 p = .004), and more likely to report others in their inner speech (r (110) = .263 p = .005). Overall, there seem to be significant relationships between verbal ability and qualities of inner speech.

Disclosures: T.M. Milewski: None. **A. Gesheva:** None. **R. Antonawich:** None. **J.T. Cannon:** None. **P.T. Orr:** None.

Poster

821. Individual Differences

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 821.06/BB62

Topic: F.01. Human Cognition and Behavior

Support: Funding from Channel 4 (UK TV broadcaster)

Funding from the Beckley Foundation

Title: Dissociable effects of different strains of cannabis on the human brain's major resting-state networks

Authors: *M. B. WALL[1,2,4], R. A. POPE[2], T. FREEMAN[2], C. MOKRYSZ[2], C. HINDOCHA[2], W. LAWN[2], M. BLOOMFIELD[3,5], A. MOSS[2], D. J. NUTT[4], H. V. CURRAN[2];
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Abstract: Two main constituents of cannabis are delta-9-tetrohydrocannabinol (THC) and cannabidiol (CBD). THC is the primary psychedelic component, while CBD may buffer the user somewhat against the effects of THC, and be therapeutically useful. Recent evidence has suggested that relatively new strains of cannabis that are high in THC and contain little or no CBD may be associated with negative effects of cannabis use (addiction, psychosis). Two strains of cannabis were tested against placebo in a double-blind three-way crossover design (N=17), and their effects on the brain's major networks examined using resting-state fMRI. One strain had 13% THC and <0.1% CBD, the second had 6.5% THC and 8% CBD; double the quantity of the second was administered so that total THC content was the same for both conditions. Placebo cannabis contained no psychoactive compounds but contained terpenines so it smelled the same as active cannabis. Seed-based functional connectivity analyses were used to examine effects in the Default-Mode Network (DMN; posterior cingulate seed-region), the Executive Control Network (ECN; posterior cingulate seed, anticorrelation) and the salience network (anterior insula seed). The two active strains produced relatively comparable effects on the DMN, showing network disruption in the hippocampus and superior parietal regions, relative to placebo. Effects on the ECN were also similar, with disruption in the left dorso-lateral prefrontal cortex (DLPFC). However, effects on the salience network were markedly different, with the 'balanced' (THC+CBD) strain showing minimal effects, and the pure THC strain producing widespread disruption of the network in orbitofrontal cortex, the putamen, left DLPFC and the frontal pole. Subsequent ROI analysis of these regions showed strong correlations between the posterior cingulate DMN activity, and subjective measures of the drug effect (visual analogue scale items: 'high', 'feel drug effect', 'dry mouth' 'enhanced auditory perception'; all $r>0.6$, all $p<0.01$) for the pure THC condition, but these relationships were not present in the balanced (THC+CBD) condition. The left DLPFC also emerged as an important region in the correlation analyses, being associated with negative subjective ratings such as 'mentally impaired' ($r=0.62$, $p=0.008$; ECN) and 'paranoid' ($r=0.67$, $p=0.003$, salience network) in the pure-THC strain, but not in the balanced strain. These results suggest the posterior cingulate may be a key region involved in the subjective effects of cannabis, while disruption in the left DLPFC may contribute to more negative effects. Also, CBD does appear to buffer the user from the effects of THC.

Disclosures: **M.B. Wall:** A. Employment/Salary (full or part-time):; Imanova Limited. **R.A. Pope:** None. **T. Freeman:** None. **C. Mokrysz:** None. **C. Hindocha:** None. **W. Lawn:** None. **M. Bloomfield:** None. **A. Moss:** None. **D.J. Nutt:** None. **H.V. Curran:** None.

Poster

821. Individual Differences

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 821.07/BB63

Topic: F.01. Human Cognition and Behavior

Support: DGAPA PAPIIT IN223314 to AERC and IN224314 to OPG.

Title: Years of use of marijuana and episodes of consumption during the last month reduce efficiency in procedural learning

Authors: *U. CABALLERO SÁNCHEZ[1], T. V. ROMÁN-LÓPEZ[1], H. I. GUILLERMO-MONTIEL[1], C. B. ROSAS-ESCOBAR[1], E. I. ORTEGA-MORA[1], J. A. GONZÁLEZ-BARRIOS[2], O. PROSPERO-GARCÍA[3], A. E. RUIZ-CONTRERAS[1];
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Abstract: Procedural learning is the acquisition, gradual and unconscious, of new abilities which operate automatically. It has been observed that marijuana consumption, together with Human Immunodeficiency Virus, decreases procedural learning. However, marijuana's effect alone was not reported to modify procedural learning. One of the marijuana active components, the Δ9-THC, binds to cannabinoid receptor 1 (CB1) which is widely distributed in the brain, including the striatum, cerebellum and hippocampus. These areas have been associated with procedural learning. The aim of this study was to test if variables such as the onset age of marijuana consumption (less than 17 vs. 17 or more years old), the number of years of consumption (less vs. 6 or more years) and the mean number of episodes of consumption for a month during the last six months (less vs. 30 or more episodes), affect procedural learning. Marijuana consumers solved the mirror drawing task during six trials. This task consisted in drawing a line within the double contour of a star. Subjects were not able to watch their own hand, the pencil or the star directly, only through the mirror. Completion time of drawing was the dependent variable. The onset age of marijuana consumption did not have an effect on procedural learning. Marijuana consumers with six or more years of consumption had longer completion times than subjects with less than six years of marijuana consumption. Also, completion time was longer for those

subjects whose consumption of marijuana was more than 30 episodes than those who consumed less than 30 episodes. All these effects were not due to a generalized motor slowness, which was evaluated with a control task. These results indicate that marijuana consumption diminished performance on procedural learning, i.e., when there is a prolonged consumption (i.e. 6 years or more), and when the consumption is larger than 30 episodes during a month. This study was conducted with the support of the following grant: DGAPA PAPIIT IN223314 to AERC and IN224314 to OPG.

Disclosures: U. Caballero Sánchez: None. **T.V. Román-López:** None. **H.I. Guillermo-Montiel:** None. **C.B. Rosas-Escobar:** None. **E.I. Ortega-Mora:** None. **J.A. González-Barrios:** None. **O. Prospero-García:** None. **A.E. Ruiz-Contreras:** None.

Poster

821. Individual Differences

Location: Hall A

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Program#/Poster#: 821.08/BB64

Topic: F.01. Human Cognition and Behavior

Support: DGAPA PAPIIT IN224314 to OPG and CONACYT 176196 to AERC

Title: Genetic variation of the cannabinoid receptor 1 is associated with the distraction vulnerability in marijuana users and non-users

Authors: *C. B. ROSAS ESCOBAR[1], U. CABALLERO-SÁNCHEZ[1], E. I. ORTEGA-MORA[1], H. I. GUILLERMO-MONTIEL[1], T. V. ROMÁN-LÓPEZ[1], J. A. GONZÁLEZ-BARRIOS[2], O. PROSPÉRO-GARCÍA[3], A. E. RUIZ-CONTRERAS[1];
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Abstract: Attention is the ability to select relevant information from the environment and, at the same time, to inhibit distracting or irrelevant information. The selection process can fail, during a selective attention task when a distractor appears, the efficiency is reduced. It has been reported that marijuana users are more prone to distraction when marijuana-related distractors is presented. Deltha-9-tetrahydrocannabinol (Δ9-THC) is the most studied marijuana's component, which binds to the cannabinoid receptor 1 (CB1). CB1 receptor is distributed along cerebral areas associated with attention. The CB1 is coded by the CNR1 gene. One polymorphism of this

gene, the rs2180619 (A>G), is located in a potentially regulatory region and has been associated with attention and working memory in control subjects. The present research evaluated if the polymorphisms of the rs2180619 of the CNR1 gene were associated with distraction vulnerability in marijuana users and non-users. The distraction vulnerability was measured in both groups with a Singleton Task, which evaluates "attentional capture". A main effect of genotype was found for percentage of correct responses, GG subjects had less accuracy than AG subjects, regardless of marijuana use. For reaction times, there was a significant interaction between group and genotype: the AG marijuana users had longer reaction times than AG non-users. Also, the AG marijuana users had longer reaction times than AA users. However, the marijuana use modified the effect of genotype of rs2180619, specifically in A carriers. These results suggest that G carriers are more vulnerable to distraction than AA subjects, and marijuana use modifies this relationship. This study was conducted with the support of the following grants: DGAPA PAPIIT IN224314 to OPG and CONACYT 176196 to AERC.

Disclosures: **C.B. Rosas escobar:** None. **U. Caballero-Sánchez:** None. **E.I. Ortega-Mora:** None. **H.I. Guillermo-Montiel:** None. **T.V. Román-López:** None. **J.A. González-Barrios:** None. **O. Prospéro-García:** None. **A.E. Ruiz-Contreras:** None.

Poster

821. Individual Differences

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 821.09/BB65

Topic: F.01. Human Cognition and Behavior

Support: DGAPA PAPIIT IN224314 to OPG and CONACYT 176196 to AERC.

Title: Genetic variation of the cannabinoid receptor 1 is associated with accuracy differences in working memory maintenance in marijuana users

Authors: *T. V. ROMÁN-LÓPEZ[1], E. I. ORTEGA-MORA[1], C. B. ROSAS-ESCOBAR[1], U. CABALLERO-SÁNCHEZ[1], H. I. GUILLERMO-MONTIEL[1], J. A. GONZÁLEZ-BARRIOS[2], O. PROSPÉRO-GARCÍA[3], A. E. RUIZ-CONTRERAS[1];
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Abstract: Working memory is defined as the maintenance and manipulation of information in a goal-directed behavior. It has been observed that efficiency in working memory decreases when

deltha-9-tetrahydrocannabinol (Δ9-THC) is administered. The Δ9-THC is one of the most studied marijuana psychoactive components, which binds to cannabinoid receptor 1 (CB1). The CB1 receptor is coded by the CNR1 gene. The rs2180619 (A>G) is a single nucleotide polymorphism (SNP) which is located in a potentially regulatory region of the CNR1 gene. This SNP has been associated with differential efficiency in working memory in control subjects. The aim of this research was to study if the association between rs2180619 and working memory performance was modified by the use of marijuana. Working memory was measured by means of the Sternberg Paradigm, which is mainly a maintenance task. This paradigm consists of the presentation of several sets of letters. In each set, 1, 3 or 5 letters were presented at the beginning of a trial; the subject is instructed to remember these letters. After a delay period, a sequence of individual letters is presented and the subject has to indicate if each of these letters were present or not in the initial set. Only marijuana users participated in this research. AA genotype was compared to AG or GG (G carriers) subjects. It was observed that the G carriers had a higher accuracy in the Sternberg task compared with AA subjects. These results suggest that having at least one G allele in marijuana users is associated with a higher efficiency in maintenance of information in working memory. This study was conducted with the support of the following grants: DGAPA PAPIIT IN224314 to OPG and CONACYT 176196 to AERC.

Disclosures: **T.V. Román-López:** None. **E.I. Ortega-Mora:** None. **C.B. Rosas-Escobar:** None. **U. Caballero-Sánchez:** None. **H.I. Guillermo-Montiel:** None. **J.A. González-Barrios:** None. **O. Prospéro-García:** None. **A.E. Ruiz-Contreras:** None.

Poster

821. Individual Differences

Location: Hall A

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Program#/Poster#: 821.10/BB66

Topic: F.01. Human Cognition and Behavior

Support: DGAPA PAPIIT IN223314 to AERC.

DGAPA PAPIIT IN224314 to OPG.

Title: Interaction of rs2180619 of the CNR1 gene, sex and marijuana use in executive attention

Authors: *E. I. ORTEGA MORA[1], C. B. ROSAS-ESCOBAR[2], U. CABALLERO-SÁNCHEZ[2], T. V. ROMÁN-LÓPEZ[2], H. I. GUILLERMO-MONTIEL[2], J. A. GONZALEZ-BARRIOS[3], O. PROSPERO-GARCIA[4], A. E. RUIZ-CONTRERAS[2];
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Abstract: Attention is the ability to select relevant information and, at the same time, inhibit distractor stimuli according to an objective. One way of evaluating this ability is with the Attentional Network Task (ANT), where alerting, orientation and executive attention indices are measured. In this task, the participants had to indicate the orientation of the center target arrow, among four flanker arrows. This task has two trial types: congruent (where the target and the flanker arrows are in the same orientation) and incongruent (where a conflict occurs because the target arrow is in a different orientation from the flanker arrows) trials. A conflict effect is observed reflected by a lower accuracy and longer reaction times in incongruent vs. congruent trials. Marijuana users' performance in ANT is worse than non-users. Deltha-9-tetrahydrocannabinol (Δ9-THC), the most studied component of the marijuana, is an agonist of cannabinoid receptor 1 (CB1). The CNR1 gene codes for the CB1 receptor; a polymorphism of a single nucleotide in this gene, rs2180619 (G>A), localized on a potentially regulatory region of the CNR1 gene, has been associated with addiction and, more recently, with cognitive functions. The aim of this study was to test whether efficiency in the ANT is associated with the polymorphism of the rs2180619 in marijuana users and non-users. Our results showed a main effect of genotype: A carriers showed a low percentage of correct responses in incongruent vs. congruent trials. Nonetheless, GG subjects did not present the typical conflict effect. An interaction among genotype, sex and marijuana use was observed. Only female AA marijuana users had lower percentage of correct responses for incongruent trials than female AA non-users. These results show that the alternative genotypes of rs2180619 are associated differentially with the ability to respond to the conflict in ANT, regardless of marijuana use. However, marijuana use interacts with rs2180619 and sex variables to affect performance in incongruent trials.

Disclosures: E.I. Ortega mora: None. **C.B. Rosas-escobar:** None. **U. Caballero-sánchez:** None. **T.V. Román-lópez:** None. **H.I. Guillermo-montiel:** None. **J.A. Gonzalez-barrios:** None. **O. Prospero-garcia:** None. **A.E. Ruiz-contreras:** None.

Poster

821. Individual Differences

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 821.11/BB67

Topic: F.01. Human Cognition and Behavior

Support: Evelyn F. McKnight Foundation

Arizona Alzheimer's Consortium

Title: Fractional anisotropy in the left uncinate fasciculus and the inferior cingulum differentially predict memory and executive functions in older adults

Authors: *M. B. SCHMIT, K. KAWA, A. STICKEL, L. RYAN;
Univ. of Arizona, Tucson, AZ

Abstract: Fractional Anisotropy (FA) as measured by diffusion weighted imaging is associated with white matter changes and cognitive functioning in older adults (Ryan et al. 2011). However, relatively few studies have investigated tract-specific FA values' impact on cognition. The present study investigated FA measures in three tracts - the uncinate fasciculus, the left inferior portion of the cingulum and the left superior longitudinal fasciculus (SLF)- and two cognitive tasks -memory (verbal paired associate delayed recall) and executive functioning. Letter-number sequencing was used as the measure of executive functioning because it incorporates both maintaining verbal material in working memory and task switching. FA was calculated from diffusion weighted MR images obtained in 25 directions from 38 older adults (Age 61-88 years, mean=71.6). Diffusion images were aligned using DTI-tk, which employs local tensor information for improved alignment. Tracts were defined using deterministic tractography (Wakana et al. 2007) and warped into native space for extracting FA from each tract. General linear models were created to predict delayed recall and letter-number sequencing. Predictor variables were global FA (an average of FA across all white matter), left uncinate fasciculus FA, left superior longitudinal fasciculus FA, and cingulum FA, while controlling for age and education. The letter-number sequencing model (GLM $p<.005$) showed not only global FA as a predictor ($p<.005$) but also an independent contribution of left uncinate fasciculus ($p < .005$), and left superior longitudinal fasciculus ($p<.05$). FA in the cingulum was not predictive. Delayed recall scores were significantly predicted (GLM $p < .01$) specifically by FA in the cingulum ($p<.01$) and education ($p<.05$) and not by any other factors. Global FA, left uncinate fasciculus, and left superior longitudinal fasciculus were not predictive of performance. The association between letter-number sequencing and the uncinate fasciculus may reflect the recruitment of frontal and temporal areas for the verbal nature of the task, while the frontal-parietal connections of the left superior longitudinal fasciculus mediate the working memory component. The cingulum, predictive of delayed recall, includes white matter through the temporal stem adjacent to the subiculum of the hippocampus. The relationship between FA values and cognitive performance is strongly dependent on which tract is being measured. Individual changes in memory and executive functioning with age may be mediated by white matter changes in specific regions, rather than global decline.

Disclosures: **M.B. Schmit:** None. **K. Kawa:** None. **A. Stickel:** None. **L. Ryan:** None.

Poster

821. Individual Differences

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 821.12/BB68

Topic: F.01. Human Cognition and Behavior

Support: VIDI

ERC

Title: Exploring the neurocognitive mechanisms underlying trigger failures in the stop-signal paradigm

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Abstract: The interplay between inhibition and attention is pivotal for everyday functioning. As we interact with our environment, we suppress most of the incoming information as well as prepotent responses that stand in the way of the current goal. In order to accomplish our goals, attentional resources have to be devoted to the task at hand. In this study we examine temporary fluctuations in attention in a context requiring inhibition of a preprotent response. We model so-called “trigger failures” in a stop-signal paradigm: Subjects are asked to respond to a left or rightward pointing arrow presented on a monitor. Occasionally, auditory tones (the stop signal) prompt the subjects to withhold their response to the corresponding arrow. In order for the stop signal to elicit the appropriate suppression of the motor response, sufficient attentional resources have to be allocated to incoming auditory information. Fluctuations in this allocation of attention contribute to the success or failure to inhibit prepotent responses in this paradigm. Here, we investigate the most extreme fluctuations in attention, in which the suppression of the prepotent responses is not initiated due to a lapse in attentional focus towards the auditory stop-signal. We use a recently developed Bayesian method which allows us to estimate the entire SSRT distribution, as well as a trigger failure parameter which represents the individual propensity for failing to trigger the stop process. In our fMRI analyses, we replicate earlier findings linking the right inferior frontal gyrus (rIFG) to efficacy of the stopping process measured through the stop-signal response time (SSRT). Finally, we show that activity in this region can additionally be explained by individual differences in the propensity for trigger failure. In sum, these results contribute to our understanding of the intricate interplay of inhibition and attention.

Disclosures: W. Boekel: None. **D. Matzke:** None. **A. Heathcote:** None. **B.U. Forstmann:** None.

Poster

821. Individual Differences

Location: Hall A

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Program#/Poster#: 821.13/BB69

Topic: F.01. Human Cognition and Behavior

Support: IBS-R015-D1

NRF-2012H1A2A1001137

Title: Fronto-parietal networks activation reflects varying attentional demands during dual-task

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Abstract: We designed a dual-task paradigm combining concurrent verbal working memory with an oculomotor task. These two tasks are known to share common fronto-parietal (FP) networks in our brain. Two levels of memory load (5- or 10-words) and three oculomotor tasks (eye fixation, predictive & random smooth pursuit eye movement) generate different dual-task combinations. We assumed that different combinations would generate different attentional demands and accordingly require different levels of cognitive strategy under limited cortical resources. This may resulted in different neural activation patterns as well as behavioral performances during dual-task situations. To investigate this hypothesis, we measured oscillatory brain activity and phase synchronization using simultaneous EEG and MEG recording in normal subjects subdivided by their innate working memory capacity (WMC). Results showed the distinct patterns of frontal midline theta (4-6Hz) synchronization and parietal upper alpha (10-12Hz) desynchronization among the dual-task conditions during the word retention period. Findings also showed different amounts of FP alpha phase synchronization. All these findings showed individual differences between high and low WMC groups. Distinct neural networks of each oculomotor task might affect the attentional load imposed on the FP network and generate different neural activation patterns as well as behavioral performances. In conclusion, varying

attentional demands and WMC seem to affect the dynamic cortical resource allocation strategy during our dual-task scenario.

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Poster

821. Individual Differences

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Program#/Poster#: 821.14/BB70

Topic: F.01. Human Cognition and Behavior

Title: Functional and anatomical dissociation of interhemispheric transfer in human sensory systems

Authors: ***E. GENC**, P. FRIEDRICH, S. OCKLENBURG, O. GÜNTÜRKÜN;
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Abstract: Signals from sensory half-fields are processed separately in the two hemispheres but give rise to coherent percepts due to interhemispheric communication. A valid method to measure the latency of interhemispheric transmission in humans is the EEG Poffenberger paradigm. In this paradigm a lateralized stimulus is presented to observers. Based on the anatomical architecture of sensory systems, this stimulation induces an evoked potential (EP) in the contralateral followed by a second delayed EP in the ipsilateral hemisphere. This delay, computed as time difference between ipsilateral and contralateral EP, is interpreted as the interhemispheric transfer time (IHTT). Here, we used DTI and EEG measurements in different sensory domains to test whether IHTTs are related to each other and are predicted by the integrity of specific callosal segments. We determined for each participant (N=52) three different IHTTs using the EEG Poffenberger paradigm in the visual (vIHTT), auditory (aIHTT) and tactile (tIHTT) domain. In addition, DTI measurements of the same participants were acquired to estimate the microstructural integrity as indexed by radial diffusivity (RD) of specific callosal segments. A geometry-based method was applied to determine the microstructural integrity of five callosal segments. These segments were the anterior third (AT), anterior midbody (AM), posterior midbody (PM), isthmus (IS) and the splenium (SP). Statistical analyses showed that the three IHTTs were independent of each other. We found no significant correlation between vIHTT and aIHTT ($r = -.00$, $p = .98$), vIHTT and tIHTT ($r = .24$, $p = .09$) and aIHTT and tIHTT ($r = -.01$, $p = .94$). Further, we tested whether each distinct IHTT is predicted by the architecture of topographically specific callosal segments. In a multiple-regression analysis with segment

RDs as independent variable and vIHTT as dependent variable, only RD of the SP segment provided a unique contribution to the vIHTT prediction (SP segment, ß = -.39, p = .03; other segments p > .11). In contrast, for the aIHTT only the RD of the PM segment provided a unique contribution to the aIHTT prediction (PM segment, ß = -.51, p = .02; other segments p > .41). For the tIHTT only the RD of the IS segment provided a trend for a unique contribution to the tIHTT prediction (IS segment, ß = -.34, p = .07; other segments p > .66). Our study demonstrates for the first time that, for a given observer, the *in vivo* conduction velocity of callosal transmission is distinct for different sensory domains. Importantly, we showed that this dissociation also holds on the anatomical level: Each distinct callosal transmission was shaped by the layout of specific callosal connections.

Disclosures: **E. Genc:** None. **P. Friedrich:** None. **S. Ocklenburg:** None. **O. Güntürkün:** None.

Poster

821. Individual Differences

Location: Hall A

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Program#/Poster#: 821.15/BB71

Topic: F.01. Human Cognition and Behavior

Title: The effect of hemispheric asymmetry and handedness on p300 responses

Authors: *P. CHUA[1], M. TAN[1], Y. YANG[2], F. TEY[1];
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Abstract: In visual oddball studies, distinctive event-related potentials (ERPs) such elevated P300 spikes have been found to occur when a target stimulus suddenly appears during a presentation sequence of repetitive non-target images. Given the range of individual differences in hemispheric laterality, the waveform of these signals may differ between individuals (Eskikurt et al., 2013). Hemispheric asymmetries may manifest in behavioural traits such as handedness (Polich & Hoffman, 1998); thus the purpose of this study was to investigate the links between handedness and P300 readings collected during a visual oddball task. For this study, handedness was determined using the Edinburgh Handedness Inventory (Oldfield, 1971). Three groups of participants were recruited (4 left-handed, 4 right-handed and 5 ambidextrous). ERPs were recorded from up to 32 cortical sites while participants conducted the visual oddball task. Statistical analysis was conducted using the non-parametric Mann-Whitney test. Findings were correlated with the location of the cortical sites in relation to general lateralisation of brain signals. When an asymmetrical electrode layout was used (with higher concentration over the

right motor region), significant differences were found between between the right- and left-handed groups (U = 0.500, p = 0.029). However no differences were found between the right-handed and ambidextrous groups (U = 7.500, p = 0.566) or the left-handed and ambidextrous groups (U = 4.000, p = 0.190). When a symmetrical layout was used (with electrodes spread equally over the left and right hemispheres), there was no significant difference found between all the groups. Taken together, these results suggest that behavioural asymmetries (such as handedness) may provide a useful guide for determining optimal electrode placement in tasks such as the visual oddball paradigm. References Eskikurt, G., Yucesur, I., and Isoflu-Alkac, U. (2013). The effect of handedness on visual P300 responses and visual scanning pathways. *Activitas Nervosa Superior Vol 55, 38-50.* Oldfield, R. (1971). The assessment and analysis of handedness. *Neuropsychologia, Vol 9, 97-113.* Polich, K., and Hoffman, L. (1998). P300 and handedness: on the possible contribution of corpus callosal size to ERPs. *Psychophysiology, Vol 35(5), 497-507.*

Disclosures: **P. Chua:** None. **M. Tan:** None. **Y. Yang:** None. **F. Tey:** None.

Poster

821. Individual Differences

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 821.16/BB72

Topic: F.01. Human Cognition and Behavior

Title: Distinct patterns of interactions between resting state networks are related to different facets of Theory of Mind

Authors: *N. T. GALLAGHER[1], A. RIGON[2], M. M. SWIFT[3], M. C. DUFF[4], M. W. VOSS[3,2]; [1]Univ. of Iowa Dept. of Psychology, [2]Interdisciplinary Grad. Program in Neurosci., [3]Dept. of Psychological & Brain Sci., [4]Dept. of Communication Sci. and Disorders, Univ. of Iowa, Iowa City, IA

Abstract: Theory of Mind (ToM) is the ability to infer others' beliefs, feelings, and intentions to better understand and predict their future behaviors. For humans, the ability to execute effective social interactions is a crucial part of individual well-being and quality of life. ToM represents a pivotal component of this process and ToM deficits are also the hallmark of several psychiatric disorders. ToM can be assessed with tasks presented in different modalities (e.g., self-report vs. visual), often with markedly different results in behavioral performance. In the current study, we sought to investigate the reasons behind such modality differences by examining whether performance on a visual task and a self-report task are associated with distinct or similar

functional brain networks. To this end, we administered to a non-clinical population (N=20) of young adult females 1) the Interpersonal Reactivity Index (IRI) Perspective Taking scale, and 2) the Reading the Mind in the Eyes (EYES) test. As commonly found in ToM tasks, we noticed considerable inter-individual variability both in IRI scores (M=19.9, SD=4.58, range=12-27) and EYES performance (EYES= 28.45, SD=2.1, range=24-32). We chose to use resting state fMRI (rs-fMRI) to examine patterns of functional connectivity (FC) at rest: due to its task free nature, rs-fMRI is an ideal technique to explore how a given trait (e.g., ToM ability) corresponds to different patterns of brain activity. In particular, we examine FC in the Default Mode Network (DMN), Mirror Neuron System (MNS), and frontal executive network (FEN) given their purported relationship with ToM ability. These networks were chosen due to their role in self-referential thought, understanding others' actions, and externally oriented cognition. Our results indicated that participants with higher self-reported ToM ability had greater FC between FEN and DMN (r=.545, p<.01), while EYES performance was higher in participants who had greater FC between the MNS and DMN (r=.556, p<.01). Our findings support the involvement of large-scale resting state networks (previously identified as networks contributing to ToM processing by task-related studies), working together to process ToM. In addition, the current study furthers our understanding of the way different brain systems interact and play different roles to allow the complex nature of ToM to take form, suggesting that different facets of ToM may have different neurobiological underpinnings.

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Poster

821. Individual Differences

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Topic: F.01. Human Cognition and Behavior

Support: NIMHD MD007599-28

NIDA R24 DA012136-12

Title: Amygdala and insula response to social and non-social affective scenes in women with different trauma types

Authors: *O. KLESHCHOVA[1,2], S. A. YOON[1,2], M. R. WEIERICH[1,2];
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Abstract: Interpersonal trauma (IPT) is associated with more trauma-related symptoms and greater risk of psychiatric diagnosis than non-interpersonal trauma (NPT). IPT also has been linked to distinct abnormalities in affective processing and salience detection, as well as structural and functional aberrations in the limbic system, particularly in the amygdala and insula. However, potential differences in affective processing at the level of neural circuitry between people with IPT and NPT are not known. We hypothesized that women with IPT would display greater amygdala and insula response to complex social affective scenes than women with NPT. Fourteen women with IPT, 6 women with NPT, and 11 no-trauma controls viewed affective social and non-social scenes during an fMRI scan. We performed a priori ROI analyses for the bilateral amygdala and insula, and conducted an ANOVA to test differences between the three groups. In addition, we conducted an ANCOVA between the two trauma groups with trauma type as a predictor and number of trauma-related symptoms as a covariate. Women with NPT showed decreased right insula activation to positive non-social scenes versus baseline compared with women with IPT and controls ($F(2,28)=5.51$, $p=.01$). The NPT group also displayed greater right insula activation to positive social vs. non-social scenes than the other two groups, who showed a similar response to both positive social and non-social scenes ($F(2,28)=4.49$, $p=.02$). When controlling for number of trauma related symptoms, women with NPT showed lower left amygdala response to social ($F(1,17)=6.12$, $p=.024$), particularly positive, ($F(1,17)=5.15$, $p=.037$) scenes and non-social negative scenes ($F(1,17)=4.98$, $p=.039$) than women with IPT. Counter to our predictions, salience network activity in the IPT group was more similar to controls than the NPT group. Women with NPT showed lower amygdala and insula activation to positive social and non-social scenes, respectively, suggesting that exposure to NPT might be associated with lower affective response to positive information. In addition, the NPT group displayed less affective response to non-social negative information. Together, these data suggest that non-interpersonal trauma might be associated with greater affective blunting compared with interpersonal trauma.

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Poster

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Topic: F.01. Human Cognition and Behavior

Support: MOST103-2420-H-009-006-MY2

Title: Culture traits affect our perceptual processing to social cues

Authors: *Y.-C. LEE[1], P.-S. HO[2,3], H.-L. LIU[4], P.-C. SHIH[1], H.-W. HUANG[5], C.-M. HUANG[2,3], C.-T. WU[1,6];
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Abstract: Culture is an important predictor that reflects how people interact with their environments and gregarious societies, which seems to be capable of further shaping how people perceived the outer world. Increasing evidence suggests that individuals from collectivistic cultures are more sensitive to relationships between objects and their contexts, whereas individuals from individualistic cultures are more sensitive to focused objects of the environment. However, how cultural traits influence an individual's social attention and its underlying neural mechanisms remains unclear. To address this issue, we enrolled participants who showed varying degree of individualism and collectivism, as defined by the Singelis Self-Construal Scale (Singelis, 1994), to participate in a gaze flanker task during fMRI scan. For each trial, we presented a central face gazing toward the left or the right side simultaneously flanked with 4 peripheral faces gazing toward the same (congruent condition) or different (incongruent condition) direction of the central face. Participants were instructed to pay attention to the central face and respond its gaze direction with button presses. Our results showed that, when dealing with incongruent situations, both groups (individualistic and collectivistic participants) exhibited an increased hemodynamic response in the dorsolateral prefrontal cortex. Notably, only the collectivistic group showed significant signal changes in brain regions implicated in both error detection/conflict monitoring and attentional processing of visual stimuli, including the anterior cingulate cortex, the inferior frontal gyrus, and the occipital lobe. These findings provide evidence that our perceptual processing to social cues are modulated by cultural traits and suggest that people from a collectivistic culture indeed are easier to be affected by the interrelationship between objects and their contexts than people from an individualistic culture.

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Poster

821. Individual Differences

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Program#/Poster#: 821.19/BB75

Topic: F.01. Human Cognition and Behavior

Title: Culture-related differences in the contextual processing of visual scene: an fMRI study

Authors: *P.-S. HO[1,2], Y.-C. LEE[3], H.-L. LIU[4], D.-J. TSENG[1,2], Y.-J. CHANG[1,2], R. DOOLE[1], C.-T. WU[3,5], H.-W. HUANG[6], C.-M. HUANG[1,2];
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Abstract: There is growing interest in how differences in culturally based social and cognitive environments influence the way people perceive the visual world. Converging behavioral and neuroimaging evidence indicates that individuals from collectivistic/interdependent sociocultural system are more sensitive to contextual information, whereas individuals with individualistic/independent representation have a tendency to process focal and discrete objects of the environment. In the present study, we employed functional MRI to investigate whether the cultural values of collectivism and individualism influence the contextual processing of visual scenes by manipulating the congruence of the pictures presented. Each participant's degree of endorsement of individualistic and collectivistic values was assessed by their self-report on the Singelis Self-construal Scale (Singelis, 1994). Both individualistic (IND) group and collectivistic (COL) group were scanned in this event-related-design experiment as they made animacy judgments for the scenes in which the salient object was either congruent or incongruent with the background. We found that COL group showed greater activity in bilateral occipital complexes than IND group when viewing incongruent pairs. The result suggests that, when the scenes were incongruent, COL group may have devoted more brain and/or cognitive resources to object processing due to their enhanced sensitivity to the entire scene. This finding provides clear neuroimaging evidence that cultural differences in ventral visual function are not only limited to variations in attentional focus on objects and backgrounds separately, but also associated with variations in processing of semantic relationships between object and contextual information during visual recognition.

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Poster

821. Individual Differences

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Topic: F.01. Human Cognition and Behavior

Title: Neural responses to masked and unmasked threat faces in children at risk for anxiety

Authors: *A. D. GILMORE, B. C. TABER-THOMAS, E. AUDAY, X. FU, K. E. PEREZ-EDGAR;
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Abstract: Behavioral inhibition (BI) in young children is a temperamental trait characterized by social withdrawal, attention bias towards threat, and risk for anxiety (Fox et al, 2001; Pérez-Edgar & Fox 2005). Attention bias toward threat may moderate the association between BI and risk for anxiety (Pérez-Edgar et al., 2013; Bar-Haim et al., 2007). Attention bias toward threat is often quantified using the dot-probe task (Mogg & Bradley, 1999), which presents two faces simultaneously (either neutral-neutral or a neutral-threat pair), for 500ms (supraliminal) or 17ms (subliminal), followed by a probe. Neuroimaging research has found that anxious individuals show greater engagement of prefrontal regions involved in emotion regulation for supraliminal threat (Monk et al., 2006; Telzer et al., 2008), and greater activation of limbic regions involved in emotion processing and salience detection for subliminal threat (Monk et al., 2008). No study has compared neural responses to subliminal and supraliminal threat in individuals varying in level of anxiety or risk, which has the potential to inform our understanding of the neural processes underlying threat bias. Participants were children, ages 9-12 (Current N=29, 17 female, M_{AGE}=11.27), screened for behavioral inhibition (BI) as part of an ongoing study examining the role of early temperament and attention in the emergence of anxiety. Participants completed supraliminal and subliminal dot probe in a 3T MRI scanner. Functional imaging data were preprocessed and analyzed in SPM8 and the MarsBaR toolbox. Results: Attention bias was not significant across the sample (p=.46) and did not differ between BI groups (p=.57). Contrasting subliminal threat versus neutral trials, BI was positively correlated right cerebellar activation (r=.410 p=.024) and negatively related to left dlPFC activation (r=-.603 p<.001). Comparing the subliminal to supraliminal tasks, cerebellar response to subliminal threat related to greater supraliminal threat bias (r=.678 p=.045) and less dlPFC activation to supraliminal threat-

congruent trials (r=-.547 p=.023). Greater left dlPFC activation to subliminal threat negatively correlated with right dlPFC activation in supraliminal incongruent-versus-congruent trials (r=-525 p=.007). Previous studies have investigated neural correlates of subliminal attention bias and conscience attention bias separately in anxious individuals. Analyzing both subliminal and conscious response to threat cues between behavioral inhibited children and non-behaviorally inhibited children may better clarify the neural processes underlying biased attention to threat and development of anxiety.

Disclosures: A.D. Gilmore: None. **B.C. Taber-Thomas:** None. **E. Auday:** None. **X. Fu:** None. **K.E. Perez-Edgar:** None.

Poster

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Topic: F.01. Human Cognition and Behavior

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Title: Intrinsic functional connectivity correlates of frontal EEG asymmetry and risk for anxiety

Authors: *B. C. TABER-THOMAS, P. GALINSKY, A. GILMORE, N. THAI, S. MORALES, K. E. PEREZ-EDGAR;
Pennsylvania State Univ., University Park, PA

Abstract: Right frontal EEG asymmetry is one of the strongest biomarkers of risk for psychopathology (Fox et al., 1994). Behavioral inhibition (BI) is one of the strongest behavioral predictors of anxiety (Pérez-Edgar & Fox 2005), and frontal EEG asymmetry moderates the relation between BI and later anxiety_among BI (but not non-BI) children, greater right asymmetry relates to greater anxiety (Fox et al., 1994). However, the neural networks related to frontal asymmetry remain unknown. Furthermore, given that frontal asymmetry has distinct implications for individuals at risk for psychopathology, the underlying neural correlates may also vary. Here we examined data-driven analyses of intrinsic functional connectivity (iFC) related to EEG asymmetry in BI and non-BI children at risk for anxiety. Children (ages 9-12; N BI=18; N non-BI=26) provided resting EEG and resting-state fMRI data. From fMRI data we computed global iFC, or average iFC for each voxel to all other voxels in the brain (Martuzzi et al., 2011). Whole-brain between-subjects analyses were conducted to reveal regions where global iFC related to asymmetry across the whole sample (amygdala, motor cortex, and

precuneus) and where the global iFC-asymmetry relation was moderated by BI status (all results corrected for multiple comparisons at FDR $p<0.05$, with a height threshold of $p<0.005$). Less right asymmetry related to global iFC in amygdala, motor cortex, and precuneus. More right asymmetry related to global iFC in motor and somatosensory corticies for the BI group, and in bilateral frontal pole and left middle temporal gyrus for the non-BI group. These global iFC regions were then used as seeds in seed-based iFC analyses to reveal the broader networks related to right asymmetry across all participants (motor, amygdala, dlPFC), and only in the BI (somatosensory, amygdala, insula, striatum) or non-BI (lateral prefrontal, parietal, and temporal corticies) groups. Of the 11 regions where iFC related to right asymmetry in the BI group, 10 were in the limbic lobe. Of the 18 regions where iFC related to right asymmetry in the non-BI group, only 1 fell within the limbic lobe. Right frontal asymmetry related to a common intrinsic brain network across all participants that included limbic, motor, and prefrontal regions. For BI children, right asymmetry was more strongly related to limbic iFC while for non-BI children right asymmetry was more strongly related to lateral cortical iFC. These findings suggest that the neural correlates of EEG asymmetry differ among BI and non-BI children, and these distinct neural networks may be an underlying mechanism for individual differences in risk for anxiety.

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Poster

821. Individual Differences

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 821.22/BB78

Topic: F.01. Human Cognition and Behavior

Title: Breakfast consumption and mental rotations performance

Authors: *P. T. ORR[1,2], J. L. BACHMAN[3];
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Abstract: Breakfast consumption is known to play an important role in the academic performance of young children and adolescents. Some propose that these cognitive effects of breakfast are due to increased availability of glucose to the central nervous system. Experimental fasting has demonstrable effects on mental rotation ability, but it is not known if these fasting-related effects are differentially affected by different types of breakfasts. In the current study, 12 participants (6 male) were asked to fast overnight and were subsequently tested on mental rotations on three separate occasions. Approximately one hour prior to testing, participants were

fed a low glycemic index, high glycemic index, or no breakfast. Blood glucose levels were measured at the start of every session and these measurements continued at 30 minute intervals. Type of breakfast had a significant effect on blood glucose levels immediately prior to behavioral testing ($F(2, 18) = 12.136$, $p < .001$) and on overall accuracy during mental rotations task ($F(2, 20) = 4.424$, $p = .026$). Further, there was a significant interaction between sex and type of breakfast on mental rotations accuracy ($F(2, 20) = 6.147$, $p = .008$). Females had lower accuracy on the mental rotations task after eating a low glycemic index breakfast. These data offer support for the hypothesis that glucose availability is a critical factor mediating the relationship between breakfast and cognitive ability and suggest that there may be sex-specific relationships between breakfast consumption and cognition.

Disclosures: P.T. Orr: None. **J.L. Bachman:** None.

Poster

822. Behavioral Training and Social Cognition

Location: Hall A

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Program#/Poster#: 822.01/BB79

Topic: F.02. Animal Cognition and Behavior

Support: NSERC

Title: Social company modulates conditioned disgust in male rats

Authors: *N. BOULET, C. J. CLOUTIER-DUKE, M. KAVALIERS, P. OSSENKOPP; Western Univ., London, ON, Canada

Abstract: Disgust responses are observed across numerous species and are considered to have their origins in defenses against toxicity and pathogens. Disgust encompasses a wide range of behavioral responses, including those associated with vomiting or emesis. Non-emetic species, such as the rat, lack the musculature and brainstem pathway needed to expel harmful toxins. Instead, rats display distinctive disgust reactions when given a taste previously paired with sickness. Of these disgust reactions, the gaping reaction is the most reliable. Results of comparative, evolutionary and neurobiological investigations have supported the gape display as an indicator of disgust. It has been further shown that, in the absence of illness, exposure to a context previously paired with a toxin elicits gaping in rodents. Here we consider whether social factors can also serve as cues for the display of anticipatory disgust in rats. Over 4 conditioning days (72 hours apart), 44 naïve male Long-Evans rats were intraperitoneally injected with either 128 mg/kg LiCl (0.15M) or 0.9% isotonic saline (NaCl). Each of these treatment groups was

further subdivided into LiCl and NaCl-treated rats exposed to either the conditioning context only (Groups LiCl-Alone and NaCl-Alone), or exposed to the conditioning context plus a specific stimulus rat (Groups LiCl-Social and NaCl-Social).72 hours following the last conditioning day, rats were tested over 2 drug-free test days (48 h apart). On test day 1, rats were re-exposed to the stimulus rat in a novel striped context for 10 minutes while aversive behaviors were analyzed. During test day 1, a significant effect of conditioning group (social versus alone) on gaping ($p < .01$) was observed. The mean number of gapes for the LiCl-Social condition, significantly differed from the mean number of gapes for the LiCl-Alone condition ($p = 0.013$). However, on test day 2, when the rats were placed back in the conditioning context in the absence of the social partner, there were no significant differences between groups. The LiCl-Alone group also showed significantly more aversive behaviors on test day 2 relative to test day 1 ($p = 0.007$). Social behaviors were also analyzed and it was determined that the LiCl-Social group initiated significantly more social interactions with their social stimulus compared to the NaCl-Social group ($p = 0.021$). Our results demonstrate that, in a distinct context, a rat treated with LiCl in the presence of a familiar social partner displays more gaping reactions, compared to LiCl treated rats paired with an unfamiliar social partner. These findings suggest that social factors can both elicit and modulate anticipatory disgust reactions.

Disclosures: **N. Boulet:** None. **C.J. Cloutier-Duke:** None. **M. Kavaliers:** None. **P. Ossenkopp:** None.

Poster

822. Behavioral Training and Social Cognition

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 822.02/BB80

Topic: B.07. Synaptic Transmission

Title: Patterns of oxytocin receptor expression in the rodent central nervous system

Authors: ***M. MITRE**[1], B. MARLIN[2], S. NORDEN[3], E. MORINA[3], C. AOKI[5], R. FROEMKE[4], M. CHAO[6];
[1]Physiol. and Neurosci., [2]NYU Sch. of Med., New York, NY; [3]New York Univ. Sch. of Med., New York, NY; [4]New York Univ. Sch. of Med., new York, NY; [5]NYU Ctr. for Neural Sci., New York, NY; [6]new York Univ. Sch. of Med., New York, NY

Abstract: Oxytocin is an essential neuropeptide that regulates social behaviors such as maternal care and parent-infant bonding. Peripheral release into the systemic circulation is responsible for its classical physiological functions of milk ejection and initiation of parturition, whereas central

release seems to modulate social cognition in animals, and has been implicated in maternal behavior, aggression, anxiety, fear, interpersonal trust, autism spectrum disorders, schizophrenia, and depression. It is believed that the forebrain distribution of oxytocin receptors is responsible for its effect in modulating certain social behaviors and cognition; however, the precise expression pattern of oxytocin receptors and the downstream effects of oxytocin receptor signaling both remain unclear. We examined the distribution of oxytocin receptors in the rodent brain and their mechanism of action. To follow the distribution of the oxytocin receptor, we generated antibodies against unique sequences of the mouse oxytocin receptor and identified cells expressing these receptors in the lateral septum, cortex, medial amygdala, hippocampus, and hypothalamus of male and female mice. No labeling was detected in oxytocin receptor knockout animals. We addressed which cell types and neural circuits are directly sensitive to oxytocin and also used oxytocin-ires-cre mice to determine the projection pattern of oxytocin fibers. We found that the receptors were largely expressed on inhibitory neurons, and using electron microscopy, we identified the receptor localized in axons and at synaptic terminals. Work in the Froemke lab has determined that parental experience interacts with oxytocin-based neuromodulation to affect the response of neural circuits of the adult mouse auditory cortex to neonatal vocalizations (Marlin et al. Nature, 2015). In particular, the left auditory cortex is functionally sensitive to oxytocin for the expression of pup retrieval behaviors in females. Interestingly, we have found that oxytocin receptor expression in left auditory cortex is higher than right, both at the protein and mRNA level, and this might be part of the cellular mechanism for specialized processing of pup calls. This evidence suggests that oxytocin modulation in cortex (and perhaps other brain regions) is important for control of local inhibition, providing a potential mechanism by which oxytocin regulates perceptual salience of social information.

Disclosures: **M. Mitre:** None. **B. Marlin:** None. **S. Norden:** None. **E. Morina:** None. **C. Aoki:** None. **R. Froemke:** None. **M. Chao:** None.

Poster

822. Behavioral Training and Social Cognition

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 822.03/BB81

Topic: F.02. Animal Cognition and Behavior

Support: FAPESP 2013/14466-1

UNINOVE CAPES PROSUP

Title: Study of post-pubertal social behaviors in males and females coming from maternal hypothyroidism: a link for neurodevelopmental aspects in autism-related conditions?

Authors: *C. A. PENATTI[1], J. C. SILVA[2], M. O. RIBEIRO[3], G. GIANNOCCO[4]; [2]Postgraduate Program in Med., [1]UNINOVE - Univ. Nove De Julho, São Paulo, Brazil; [3]Ctr. for Hlth. and Biol. Sci., Mackenzie Presbyterian Univ., São Paulo, Brazil; [4]Biol. Sci., UNIFESP - Federal Univ. of São Paulo, São Paulo, Brazil

Abstract: Subtle maternal thyroid dysfunction and thus subclinical maternal hypothyroidism may facilitate fetal neurodevelopmental disarrangements, which share similarities to some of the cognitive and behavior alterations manifested in the autism spectrum disorders (ASD). To date, however, there are few studies, which approach in detail the many aspects in sociability and oral communication of the post-adolescence individuals and their sex differences subjected to maternal hypothyroidism during pregnancy. Using a C57black6 mouse model of discrete maternal hypothyroidism, we investigated the social interaction of both male and female matched-offspring after puberty across several animal behavioral paradigms to look for differences in motor locomotion, anxiety, maternal care, offensive aggression and vocalization based on innate social behavior display for that mouse strain. Although there were no changes in motor locomotion and offensive aggression, we show that first generation male but not first generation female offspring from hypothyroid dams has increased anxiety levels tested at post-pubertal age using plus-maze paradigm when compared with control offspring. In addition, they displayed reduced total vocalizations towards females mainly due to the lack of emitted complex harmonic ultrasounds in a sex-oriented setting. In order to look for specific differences in the display of maternal behavior regardless of pregnancy status, we used the paradigm of foster mothers. First generation female descendants at post-pubertal age from discrete maternal hypothyroidism condition spent less time and provided less care towards the three-day old foster pups when compared with age-matched controls. Accordingly, these same females born from discrete hypothyroidism-induced dams demonstrated insufficient performance in the nest-building paradigm, which may indicate diminished sense for self-care and wellness. Thus, our findings strongly suggest that subtle maternal hypothyroidism during early pregnancy may facilitate social behavior disarrangements in the offspring in a wide array of animal behavior display in a sex-dependent manner. Moreover, fine aspects of altered social behaviors manifest at later ages such as in post-puberty and late adolescence as well as in adult life in both sexes. Finally, we speculate that our experimental behavioural findings correlate with the neuropsychological manifestations in ASD and may favor medical and psychological advances in understanding children's neurodevelopment among the ASD individuals.

Disclosures: **C.A. Penatti:** None. **J.C. Silva:** None. **M.O. Ribeiro:** None. **G. Giannocco:** None.

Poster

822. Behavioral Training and Social Cognition

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 822.04/BB82

Topic: F.02. Animal Cognition and Behavior

Title: Social involvement modulates the response to novel and adverse life events in mice

Authors: *A. LEVINE[1], S. GRULEAU[2], L. COLNAGHI[1];
[1]Columbia Univ., New York, NY; [2]Neurosci., CAMH, Toronto, ON, Canada

Abstract: In life, we tend to experience situations differently in the presence or absence of social involvement. This is especially important in relation to how we perceive adverse life events since negative experiences play a determining role in the pathophysiology and time of onset of mental illness. However, not all people who experience adverse events go on to suffer physical and emotional negative consequences that lead to psychiatric conditions, and among the various genetic and environmental factors that could mitigate the potential negative outcome of adverse events exposure, social involvement is one of them. For example, living conditions with greater social involvement, such as neighborhoods with higher average household occupancy and churches per capita, are associated with a lower incidence of mental disorders. While increased perceived interpersonal social support ameliorated the pathogenic influence of exposure to traumatic life events on psychopathology, enhancing individuals' general mental and physical well-being, both in daily life and upon exposure to negative life events. Finally, low social support is one of the most common post-event risk factors for developing post-traumatic stress disorder. Together, these findings support the idea that the response to negative experiences may be affected by social involvement. However, how social involvement confers protection against negative experiences remains poorly understood and a neuronal mechanism for this effect remains to be elucidated. In this work we set out to examine, in a mouse model, whether social involvement modulates the response to an adverse environment or event and whether it changes the way these events are registered in the brain to affect future behavior. We therefore examined whether mice respond to adverse experiences differently in the presence and absence of cage-mates in several behavioral tests: (a) exposure to a novel well-lit new environment, (b) standard elevated plus maze (EPM) test following one habituation trial, (c) exposure to a strong foot-shock during contextual fear conditioning. We find that social involvement is associated with increased movement when mice are exposed to a new environment, increase in time spent in the open arms of the EPM after an obligatory exposure to the EPM open arm and decreased freezing time in response to a foot shock as well faster fear extinction. This is a first description of a mouse model that demonstrates that social involvement plays a role in mitigating adverse life events.

Disclosures: **A. Levine:** None. **S. Gruleau:** None. **L. Colnaghi:** None.

Poster

822. Behavioral Training and Social Cognition

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 822.05/BB83

Topic: B.07. Synaptic Transmission

Support: NS24067

MH64070

Title: Oxytocin neuromodulation of pyramidal cells in CA2

Authors: ***N. N. TIRKO**[1], M. MITRE[2], B. J. MARLIN[2], R. C. FROEMKE[2], M. V. CHAO[2], R. W. TSIEN[1];
[1]NYU Neurosci. Inst., [2]Skirball Inst., NYU Sch. of Med., New York, NY

Abstract: Oxytocin neuromodulation plays important roles throughout the mammalian brain, in many cases influencing social behavior. We have seen robust oxytocin receptor (OTR) expression in CA2, a distinct hippocampal area that is critical for social memory in mice. We also have evidence that CA2 is directly targeted by axonal projections from oxytocin-producing cells of the periventricular nucleus, highlighting the potential significance of the peptide in this region. In many cases oxytocin modulates inhibitory cell function exclusively, leading to the suggestion that interneurons expressing OTR might even be considered as a distinct category of interneurons. Direct actions of oxytocin on excitatory neurons have rarely been seen, but here we report that very scenario in CA2. In this particular area, unlike CA1, we find that OTR activation dependably excites pyramidal cells, as well as neighboring interneurons. Whole-cell recordings were made from CA2 pyramidal cells, identified by their distinct electrophysiological and morphological properties. We find that application of a selective oxytocin receptor agonist (TGOT) depolarizes CA2 pyramidal cells (by ~5 mV; 100% of cells recorded) and also increases membrane resistance, R_m (by ~75 MOhm). Consequently, cell excitability is increased as indicated by elevation of action potential (AP) frequency upon depolarization by step current injection. Additionally, the shape of APs changes significantly. Spike amplitude decreases and half-width widens, while the incidence of spontaneous spike doublets and bursts increases. The OTR is a G_q-protein coupled receptor that is poised to activate the phospholipase C (PLC) pathway. As might be expected, inhibition of PLC prevented the TGOT-induced pyramidal cell depolarization and change in AP shape. However, inhibition of the downstream enzyme protein

kinase C (PKC) only blocked the change in AP shape, not the depolarization. We hypothesize that OTR activation of PLC is upstream of two effects: first, inhibition of an outward potassium current, which increases R_m and permits cell depolarization, and second, activation of PKC, which is known to phosphorylate sodium channels and lower peak currents, thus reducing AP amplitude. These findings help clarify the effects of oxytocin on CA2 pyramidal cell behavior and thus set the stage for addressing the more general question of how oxytocin activity in CA2 alters hippocampal circuit function and social behavior.

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Poster

822. Behavioral Training and Social Cognition

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Topic: B.07. Synaptic Transmission

Support: NIH Grant F31MH100891-01A1

NIH Grant R15MH102807

Title: Oxytocin in the bed nucleus of the stria terminalis and central amygdala regulates social behavior in sex-specific ways in rats

Authors: *K. M. DUMAIS, A. G. ALONSO, T. C. GILLESPIE, D. CHO, R. BREDEWOLD, A. VEENEMA;
Psychology Dept., Boston Col., Chestnut Hill, MA

Abstract: Oxytocin (OT) is a neuropeptide known to regulate social behavior in rodents and humans in sex-specific ways. This may be due to sex differences in the brain OT system. In support, we recently found robust sex differences in OTR binding densities in several forebrain regions of the rat, with higher densities observed in males over females. Here, we aimed to determine whether sex differences in OTR binding density (i) are involved in sex-specific regulation of social behavior and (ii) are associated with sex-specific OT release in the brain. We selected two brain regions: a region which shows a robust sex difference in OTR binding (the bed nucleus of the stria terminalis; BNST), and a region which shows no sex difference in OTR binding (the central amygdala; CeA). We investigated the sex-specific role of OT in the BNST and CeA in regulating social recognition (the ability to discriminate between a novel and familiar

rat) and social investigation (amount of time spent investigating a novel rat), as these behaviors are important for appropriate social functioning. We found that OT regulates social behavior in sex-specific ways, irrespective of a sex difference in OTR binding density. In detail, exogenous OT injected in the BNST prolonged social recognition in males, but not in females. Moreover, a specific OTR antagonist injected in the CeA reduced social investigation in males, but not in females. We next examined whether these behavioral effects are due to sex differences in local OT release. Although there were no sex differences in baseline OT release in either the BNST or CeA, both regions showed sex-specific OT release patterns during social behavior. Specifically, males showed higher OT release in the BNST during social recognition compared to females. Moreover, OT release in the CeA correlated positively with social investigation time in females, but not in males. In conclusion, the OT system shows idiosyncratic sex differences in the BNST and CeA associated with sex-specific regulation of social behavior. These results further suggest that males may be more susceptible to OT modulation in mediating social recognition in the BNST and social investigation in the CeA.

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Poster

822. Behavioral Training and Social Cognition

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 822.07/BB85

Topic: F.02. Animal Cognition and Behavior

Support: Simons Foundation grant ##204340

MIND Institute

Title: 16p11.2 deletion mice display cognitive deficits in touchscreen learning and novelty recognition tasks

Authors: *M. YANG[1], F. C. LEWIS[2], G. M. FOLEY[2], M. S. SARVI[2], J. N. CRAWLEY[2]; [1]MIND Institute, Dept. of Psychiatry and Behavioral Sci., [2]UC Davis Sch. of Med., Sacramento, CA

Abstract: Deletion of a ~600 kb region in chromosome 16p11.2 is found in approximately 0.4% of people with intellectual disability. Approximately 18% of 16p11.2 deletion carriers are diagnosed with autism. We previously reported that the Dolmetsch line of 16p11.2 heterozygous

(+/-) mice exhibited a robust novel object recognition deficit, normal social approach and juvenile reciprocal social interactions, and impaired social sniffing and ultrasonic vocalizations during male-female interactions, along with normal general health, olfaction, anxiety-like behaviors, and locomotion. The present study extended our previous findings on novel object recognition to additional novelty recognition tasks dependent on different neuroanatomical regions. Pairwise visual discrimination and reversal tasks using the Bussey-Saksida operant touchscreen equipment was used to evaluate cortical-dependent recognition learning and memory. Robust learning deficits and cognitive inflexibility were detected in the touchscreen test. In the acquisition phase of the pairwise visual discrimination task, 16p11.2 +/- required significantly more training days than their wildtype littermates (+/+) to reach criterion, and made more choice errors and more correction errors than +/+. In the reversal phase of pairwise visual discrimination, all +/+ reached the criterion of 85% choice accuracy, whereas most of the +/- failed to reach criterion by the 30-day cut-off. +/- also made more correction errors without making more choice errors, indicating cognitive inflexibility. Contextual and cued fear conditioning, a hippocampal and amygdala-dependent task, revealed no genotype differences. Robust novel object recognition deficits were replicated in two cohorts of 16p11.2 +/- mice, confirming previous findings. A similarly robust deficit in object location memory was discovered in +/-, indicating impaired spatial novelty recognition. Generalizability of recognition task deficits in 16p11.2 deletion mice was further tested with the preference for social novelty task. +/- exhibited impaired preference for social novelty when the familiar mouse and the unfamiliar mouse were of the same strain (129Sv/ImJ), but not when the two stimulus mice were of two genetically distant strains (129Sv/ImJ and C57BL/6J), indicating a mild deficit in social recognition. These several cognitive phenotypes in the Dolmetsch 16p11.2 deletion mice are consistent with cognitive deficits in humans with 16p11.2 deletion syndrome, and support the use of 16p11.2 deletion mice as a model system for discovering biological mechanisms underlying intellectual disabilities in 16p11.2 deletion syndrome.

Disclosures: **M. Yang:** None. **F.C. Lewis:** None. **G.M. Foley:** None. **M.S. Sarvi:** None. **J.N. Crawley:** None.

Poster

822. Behavioral Training and Social Cognition

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 822.08/BB86

Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant 1R01GM100768-01A1

Title: GWAS of foraging behavior in *Drosophila* melanogaster

Authors: *Q. YANG[1], W. CHI[2], Y. G. LEE[3], W. DU[4], C. KEMKEMER[3], S. A. TURKSON[2], M. LONG[3], X. ZHUANG[2];
[2]Dept. of Neurobio., [3]Dept. of Ecology and Evolution, [1]The Univ. of Chicago, Chicago, IL;
[4]Dept. of Biol., Wayne State Univ., Detriot, MI

Abstract: Efficient foraging behavior is crucial for the survival of an organism. Identifying the molecular and neural pathways responsible for such a trait as well as understanding the underlying genetic architecture is critical for addressing fundamental questions of economic decision-making. Here, we assessed natural variation in the foraging efficiency in 200 sequenced inbred lines of the *Drosophila* melanogaster Genetic Reference Panel (DGRP), derived from the Raleigh, NC populations. We measured the survival rate of young male flies kept individually in small chambers with unlimited, but hard to locate, food sources. Only flies that can locate food sources efficiently can survive. We observed significant variation of foraging efficiency (fifth-day survival rate varies from 0% to 100%), which was not correlated with variation in starvation resistance of these strains. We performed genome-wide association (GWA) analysis on single nucleotide polymorphisms (SNPs) and identified 89 significant SNPs (p value < 10e-5). Several of the top associated genes are highly expressed in *Drosophila* nervous system, providing promising candidates for functional examination. We found a mammalian SPAK homolog, fray, is essential for foraging efficiency. Targeted RNAi-knockdown of fray in elav-GAL4 neurons (pan-neuronal) led to severe foraging deficits in adult flies. Fray encodes serine/threonine kinase and has been previously proved to be essential for axonal ensheathment. Our findings suggest a novel signaling mechanism involving fray kinase in energy balance, and also provide insight into the adaptive evolution of foraging behaviors.

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Poster

822. Behavioral Training and Social Cognition

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 822.09/BB87

Topic: F.02. Animal Cognition and Behavior

Support: NSERC

Title: Differentially expressed glutamate and dopamine receptors in two sister species of wild birds with widely divergent cognitive abilities

Authors: *J.-N. AUDET[1], L. KAYELLO[1], S. DUCATEZ[1], E. D. JARVIS[2], L. A. O'CONNELL[3], L. LEFEBVRE[1];
[1]Biol., McGill Univ., Montreal, QC, Canada; [2]Duke Univ. and Howard Hughes Med. Inst., Durham, NC; [3]Harvard Univ., Cambridge, MA

Abstract: Research on humans and model species of lab animals suggests that glutamate and dopamine receptors have key roles in cognition. In wild birds and primates, innovation rate has been proposed as an estimate of cognition in the field, while problem-solving tasks are valid experimental measures of innovativeness in captivity. We captured wild Loxigilla barbadensis and Tiaris bicolor, two sympatric sister species that have a similar social structure, but show extreme divergence in opportunism and innovation in Barbados. We assessed their problem-solving abilities using two different tasks and quantified the expression of dopamine (D1 through D5) and glutamate receptors (NMDA, AMPA, Kainate and metabotropic) using *in situ* hybridization and RNA-Seq data. In problem-solving tasks, we found that L. barbadensis outperformed T. bicolor in an all-or-none manner. At the RNA level, the two techniques concordantly revealed that three NMDA receptors (NR1, NR2A and NR2B), but only one dopamine receptor (DRD5), were differentially expressed in the two species. Kainate, metabotropic and AMPA receptor expression did not differ between L. barbadensis and T. bicolor. This work is a first step towards identifying the molecular differences that characterize wild species that have evolved divergent cognitive strategies.

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Poster

822. Behavioral Training and Social Cognition

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 822.10/BB88

Topic: F.02. Animal Cognition and Behavior

Support: NIH AA019462

Title: Extinction of spatial navigation in the Morris water task: The effect of brief reminders

Authors: *T. DONALDSON[1], C. M. MAGCALAS[1], D. BARTO[1], K. G. AKERS[2], D. A. HAMILTON[1];
[1]Univ. of New Mexico, Albuquerque, NM; [2]Wayne State Univ., Detroit, MI

Abstract: Spatial navigation is a fundamental process for all living organisms. The Morris water task (MWT) is commonly used to investigate spatial navigation abilities of laboratory rodents. Previous studies have examined the processes involved in spatial learning and memory using the MWT, however, little is known about extinction of spatial responding or the factors that influence extinction. The current study investigated extinction of spatial responding when the platform is removed during multiple no-platform probe trials, and the influence that brief reminder treatments, in the form of platform placement, have on the rate of extinction of spatial responding. Extinction of spatial responding will be characterized by decreased accuracy in navigation and searching behavior during successive probe trials. To confirm that extinction operated in this testing situation spontaneous recovery of performance was assessed in probe trials after an hour interval of rest. Adult male Long-Evans rats were given 1, 2, or 4 days of training (12 trials per day). One day after the completion of training, rats received either a brief reminder treatment (30 sec placement on the platform in the trained location) or no treatment, followed by two consecutive 60 sec no-platform probe trials. Latency and path length to enter and time and distance spent within a critical region (50cm diameter, centered on the platform location) were measured for each probe trial. Rats that did not receive a platform placement reminder exhibited increased latency and path length to enter the critical region, while rats given the reminder did not display a robust decline in these measures across the two probe trials. While platform placement has been shown to improve some aspects of performance during subsequent training, available literature does not definitively support the idea that platform placement in the absence of active swimming to the platform can result in unambiguous spatial navigation in the MWT. Collectively, these observations suggest that extinction occurs in the MWT and that brief reminders reduce the rate of extinction.

Disclosures: T. Donaldson: None. **C.M. Magcalas:** None. **D. Barto:** None. **K.G. Akers:** None. **D.A. Hamilton:** None.

Poster

822. Behavioral Training and Social Cognition

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 822.11/BB89

Topic: F.02. Animal Cognition and Behavior

Title: Development in a novel maze-task device for macaques to explore the neural mechanisms underlying motor skill learning

Authors: R. YASUKOCHI, K. INOUE, *M. TAKADA;
Primate Res. Institute, Kyoto Univ., Inuyama, Aichi, Japan

Abstract: Motor skills are quite often use d in our daily life. Such skills are considered to be sequences of multiple elemental movements. The motor skills are usually acquired through a process of trials and errors, and, once acquired, they are kept as procedural memory for a long time. To explore the neural mechanisms underlying motor skill learning, the use of macaque monkeys is highly meritorious because of their capacity of controlling hand movements smoothly and accurately. A motor learning task for the monkeys would allow analysis of the process and pattern of progress in motor skills. Recently, we have developed a novel maze-task device for analyzing how to achieve motor skills. Our device is composed of a maze, made up of a five-by-five grid creating four vertical and four horizontal intersecting tracks, with a cursor that the monkeys can manipulate to move around the grid. After successful navigation of the cursor from the start to the goal through a correct route, the monkeys receive a small food reward. The cursor has an infrared light at the bottom for detection of its position. To test this device, a monkey was trained for 300 trials per day over a month. We then analyzed three recorded parameters: the success rate of movement, the speed of movement, and the degree of motor smoothness to reveal their changes in the process of motor skill learning. We found that the success rate of movement increased to 100% very rapidly within the first few days. By contrast, the speed of movement and the degree of motor smoothness increased more slowly and showed different patterns of improvement. The present results indicate that our maze-task device is useful for clarifying the neural mechanisms of motor skill learning.

Disclosures: R. Yasukochi: None. **K. Inoue:** None. **M. Takada:** None.

Poster

822. Behavioral Training and Social Cognition

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 822.12/BB90

Topic: F.02. Animal Cognition and Behavior

Title: Operant conditioning in neuroscience: Testing beyond motor and sensory deficits

Authors: *M. M.-M. ANDREWS[1], S. PERUZZARO[1], J. ROSSIGNOL[1,4,2], G. DUNBAR[1,4,3], M. REILLY[3,1];

[1]Neurosci., [2]Col. of Med., [3]Psychology, Central Michigan Univ., Mount Pleasant, MI; [4]Field Neurosciences Inst., Saginaw, MI

Abstract: Pre-clinical investigations into the mechanisms of neurodegenerative diseases, nervous system injuries, or pharmacological interventions primarily depend on motor and sensorimotor tasks in order to assess behavior. Consequently, deficits extending beyond motor and sensory domains may be difficult to detect and appropriately assess, resulting in missed opportunities for discovery and understanding. Capitalization upon the procedures of operant conditioning may help detect deficits that are often overlooked by some of the more conventional behavioral tests. Not only could the use of operant conditioning procedures provide an avenue to detect additional behavioral deficits, some procedures are able to control for common confounding variables, such as motor impairment. Operant techniques can provide a broad testing environment which is capable of detecting an overall decline in learning capabilities. Such procedures have been shown to detect long-term deficits in a rodent stroke model weeks after rotorod, beam balance tests, spontaneous rotation, and other such tests show recovery of function. Operant paradigms can measure complex behavior, such as impulsive decision making, perseveration, memory function, inhibition and more. Many tests that are used for neurological evaluation in humans can often be mimicked in an operant chamber, providing greater validity to the results obtained. The purpose of this poster is to present an overview of operant procedures used in neuroscience research. Matching specific operant tasks with a particular dysfunction is needed to assess potential therapies more effectively and will provide invaluable opportunities to accurately study behavior beyond the current standard of testing.

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Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.01/BB91

Topic: F.02. Animal Cognition and Behavior

Support: Supported by DHHS/NIH/NIMH/IRP.

Title: Effects of combined adenosine A2A and dopaminergic receptor antagonism on within-session concurrent discrimination learning

Authors: *B. A. CORGIAT, A.-J. PISCAPELLO, M. GORSICH, A. GARCIA, M. MISHKIN, J. TURCHI;
NIMH/NIH, Bethesda, MD

Abstract: In a previous study, monkeys were trained on a short-ITI version of a concurrent visual-discrimination learning task. Stimulus pairs were repeated not only across daily sessions but also several times within each session (with roughly 4-min ITIs). Such within-session learning is served by concomitant recruitment of both a visuo-striatal circuit and an independent visuo-rhinal circuit. Baseline discrimination learning rates are significantly reduced in this short-ITI version, from ~11 trials/pair to criterion on the 24-h ITI version of this task to ~5 trials/pair on the 4-min ITI version. Reflecting the two distinct circuits involved, systemic injections of either the dopaminergic antagonist haloperidol (HAL) or muscarinic receptor antagonist scopolamine (SCOP) impair this more rapid learning (~16 trials/ pair and ~12 trials/ pair, respectively). The HAL-induced impairment is accompanied, however, by profound increases in response latencies. To examine the cognitive effects of dopaminergic antagonism isolated from the extrapyramidal side effects, we compared the effects of separate and combined administration of haloperidol (10.0 and 17.8 μg/kg, i.m.) and the selective A2A antagonist SCH 58261 (0.32 - 1.0 mg/kg, p.o.). As previously noted, systemic administration of haloperidol alone dose-dependently increased response latencies as well as trials/pair to criterion. In contrast, co-administration of the selective A2A antagonist afforded dose-dependent attenuation of the HAL-induced increases in response latencies as well as relative number of trials to attain criterion. These findings corroborate other studies showing that selective A2A antagonism effectively counters hypoactivity induced by systemic dopaminergic blockade. Further, in the context of reports describing the complex regulation of D2 receptor profiles by adenosine, this study sets the stage for local examination of adenosine-dopamine interactions within the striatum and frontal cortices serving within-session learning.

Disclosures: B.A. Corgiat: None. **A. Piscapello:** None. **M. Gorsich:** None. **A. Garcia:** None. **M. Mishkin:** None. **J. Turchi:** None.

Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.02/BB92

Topic: F.02. Animal Cognition and Behavior

Support: Sumitomo Dainippon Pharma Co., Ltd.

Title: Dopamine D3 receptor antagonism contributes to the reversal of PCP-induced NOR deficit by blonanserin and induces cortical dopamine and acetylcholine efflux

Authors: *M. MIYAUCHI, M. HUANG, S. KWON, N. M. NEUGEBAUER, L. RAJAGOPAL, Y. OYAMADA, H. Y. MELTZER;
Northwestern Univ., Chicago, IL

Abstract: Background: Blonanserin (Blon) is an atypical antipsychotic drug (AAPD), which unlike most AAPDs, is a slightly more potent dopamine (DA) D2 than 5-HT2A antagonist. It is also a potent DA D3 antagonist, with comparable affinity to DA D2. DA D3 receptors are expressed in mesencephalic, limbic, and cortical areas, all relevant to cognition and cognitive impairment associated with schizophrenia (CIAS). It has been suggested that DA D3 receptor blockade enhances emotional processing, executive function, flexibility, and social behavior. It has previously been shown that AAPDs enhance cortical DA and acetylcholine (ACh) release, which may contribute to cognitive enhancement. The purpose of this study was to determine the ability of Blon to enhance cortical DA and ACh efflux and to clarify the role of DA D3 antagonism in that process. We also determined the ability of DA D3 antagonism to improve the novel object recognition (NOR) deficit in sub-chronic (sc) phencyclidine (PCP)-treated rats, a model of schizophrenia. Materials and Methods: Male C57BL/6 mice were used for the microdialysis study. Guide cannulae with dummy probes were aimed at the medial prefrontal cortex (mPFC) and dorsal striatum (dSTR). Dialysate samples were collected every 30 minutes and analyzed using UPLC-MS/MS methods. Following baseline sample collection, drugs were administered and neurotransmitter efflux was monitored for 180 minutes. Female Long-Evans rats received vehicle or PCP (2 mg/kg, b.i.d.) for 7 days, followed by a 7-day washout for the NOR study. Rats received DA D3 receptor antagonist, NGB2904 (NGB, 0.3, 1, 3 mg/kg) or Blon (0.3, 1 mg/kg) 30 min prior to acquisition. Another group of rats received combination of sub-effective doses (SED) of NGB (0.3 mg/kg) and SED Blon (0.3 mg/kg) 30 minutes prior to acquisition. Results: Blon, (10 mg/kg, i.p.) increased DA, norepinephrine (NE) and ACh efflux in mouse mPFC and dSTR. NGB (3 mg/kg) increased DA and ACh, but not NE efflux, in mPFC and DA efflux in dSTR. Both NGB (3 mg/kg) and Blon (1 mg/kg) improved the scPCP-induced NOR deficit. In addition, the combination of SED NGB (0.3 mg/kg) and SED Blon (0.3 mg/kg) improved the scPCP-induced NOR deficit. Discussion: The results suggested that DA D3 receptor blockade may contribute to the ability of Blon to increase cortical ACh and DA efflux, as well as to restore scPCP-induced deficit in NOR. DA D3 receptor blockade may be an important component of the efficacy of Blon to enhance neurotransmitter efflux and improve cognition. DA D3 receptor blockade alone, or as an add-on to AAPDs, may serve as a therapeutic target for the treatment of CIAS.

Disclosures: M. Miyauchi: A. Employment/Salary (full or part-time):; Sumitomo Dainippon Pharma Co., Ltd.. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Sumitomo Dainippon

Pharma Co., Ltd.. **M. Huang:** None. **S. Kwon:** None. **N.M. Neugebauer:** None. **L. Rajagopal:** None. **Y. Oyamada:** A. Employment/Salary (full or part-time):; Sumitomo Dainippon Pharma Co., Ltd. **H.Y. Meltzer:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Sumitomo Dainippon Pharma Co., Ltd., Sunovion, Janssen, Novartis, ACADIA, Ferrosan, Roche, Takeda, Pfizer, Eli Lilly, EnVivo, Reviva, Alkermes, Astellas, Jazz, Solvay, SureGene, Bristol Myers Squibb. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ACADIA, SureGene, Astra Zeneca. F. Consulting Fees (e.g., advisory boards); Lundbeck, Teva.

Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.03/BB93

Topic: F.02. Animal Cognition and Behavior

Support: COFAA Fellowship

SIP 20151173

Title: Haloperidol injected in thalamic reticular nucleus induces cognitive deficits evaluated in Morris maze in rat

Authors: *E. C. CHUC-MEZA, D. MORALES-MARTÍNEZ, G. AVILA-VELARDE; Natl. Sch. Biolog Sci. IPN, Tlalnepantla De Baz, Mexico

Abstract: Thalamic reticular nucleus (TRn) is formed by GABAergic neurons with the suitable connectivity to filter the thalamic afferent information to cortex (Crick, 1984; McAlonan et al. 2006). In the rat caudal sectors of TRn are involved in this attention process but besides rostral limbic sector could be participating in anxiety. In this regard an anxiolytic effect, measured in burying behavior and plus maze tests, was induced by chronic depletion of dopamine in this región (Picazo et al. 2009). Anxiety and memory are associated by neural structures and functional aspects. For example amygdala participates in anxiety and emotional learning and both are affected by benzodiazepins producing anxiolysis and inducing amnesia (Canteras et al. 2009). Respect to this TRn limbic sector has afferents from anterior thalamic nuclei and cingulate and retrosplenial cortices (Lozsadi, 1994; 1995) structures linked to memory (Mitchel & Dalrymple-Alford, 2006; Frankland et al. 2004) and in case of cingulate cortex also to anxiety

(Holzschneider & Mulert, 2011) . So, to evaluate the involvement of dopamine and TRn in memory, rats trained in the submerged platform option of Morris test were unilaterally canulated in rostral TRn. After recovery haloperidol (5μM in 0.4 μL) or vehicle was injected and rats were tested removing the platform (group I) o changing the platform location (group II). It was found in group I a significant reduction of time spent in the quadrant where platform was placed and an increment in latency to locate platform in group II. These results suggest the involvement of D2 like receptors in limbic TRn in modulation of cognitive abilities as spatial reference and working memories.

Disclosures: E.C. Chuc-Meza: None. **D. Morales-Martínez:** None. **G. Avila-Velarde:** None.

Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.04/CC1

Topic: F.02. Animal Cognition and Behavior

Support: Reviva research grant

Title: RP5063 reverses and prevents sub-chronic phencyclidine-induced declarative memory deficits and increased dopamine efflux in the prefrontal cortex region in C57BL/6J mice

Authors: *S. KWON, L. RAJAGOPAL, M. HUANG, E. E. MICHAEL, H. Y. MELTZER; Psychiatry and Behavioral Sci., Northwestern Univ., Chicago, IL

Abstract: Background: RP5063 is a potent, selective dopamine-serotonin stabilizer with partial agonist properties at dopamine (DA) D2, D3, and D4 receptors (Rs), and serotonin (5-HT) 5-HT1A, and 5-HT2A Rs. It also has antagonist activity at 5-HT6 and 5-HT7Rs. Although RP5063 differs from most atypical APDs, in being partial agonist at both 5-HT2A and D2Rs, its multi-receptor profile includes a number of mechanisms which have the potential to improve cognitive impairments in schizophrenia(CIS), e.g. 5-HT1A and 5-HT7 antagonism. Sub-chronic (sc) treatment with NMDAR antagonist, phencyclidine (PCP; 10 mg/kg; i.p; b.i.d. for 7 days;7 days washout), produces pervasive and enduring deficits in cognitive function, including novel object recognition (NOR), an analog of human declarative memory(DM). Atypical, but not typical APDs through an ability to enhance cortical DA efflux in the prefrontal cortex (PFC) and hippocampus, ameliorate scPCP-induced NOR deficits in rodents. Hence, we sought to determine if acute and post PCP scRP5063 could reverse the scPCP-induced NOR deficit in C57BL/6J mice as well as to determine the effect of RP5063 on neurotransmitter efflux in PFC

and dorsal striatum (STR) using microdialysis technique. Methods: Four cohorts of male C57BL/6J mice (N=8-9 per group) were used in these studies. NOR and microdialysis methodologies are described in detail elsewhere (Horiguchi and Meltzer; Psychopharmacology; 2012: 221(2):205-15 and Huang et al., J Neurochem. 2014: 128(6):938-49). Results: Acute reversal: Male C57BL/6J mice given acute RP5063 (1.0 mg/kg), but not (0.3 mg/kg) 30 min prior to beginning NOR significantly reversed scPCP-induced NOR deficit ($P<0.01$). Prevention paradigm: Animals given scRP5063 (5 mg/kg; i.p. b.i.d, 7 days) 30 min prior to each injection of PCP (10 mg/kg) on days 1-7, and tested on day 15, showed significant prevention of NOR deficit, lasting one week ($P<0.001$). Enduring reversal paradigm: Animals given scPCP followed by scRP5063 (5 mg/kg; i.p. b.i.d, 7 days) on days 15-21 and tested on day 22, showed reversal of scPCP-induced NOR deficit, again, lasting one week ($P<0.001$). Furthermore, RP5063 significantly increased DA, but not acetylcholine efflux in mPFC at 0.3, 1.0, and 3.0 mg/kg ($P<0.05$). Conclusion: These results indicate that RP5063, via multi-receptor mechanisms ameliorates scPCP-induced DM impairment. The potential of RP5063 to delay or prevent the emergence of cognitive impairment is suggested by prevention paradigm. Increasing cortical DA efflux, in one of the regions implicated in DM, may contribute to the beneficial effect of RP5063 in cognition. The clinical testing of its effects on CIS is indicated.

Disclosures: **S. Kwon:** None. **L. Rajagopal:** None. **M. Huang:** None. **E.E. Michael:** None. **H.Y. Meltzer:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research Grant. F. Consulting Fees (e.g., advisory boards); Consultant.

Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.05/CC2

Topic: F.02. Animal Cognition and Behavior

Support: Canadian Institutes for Health Research

Saskatchewan Innovation

Natural Sciences and Engineering Research Council of Canada

Title: Effects of the NMDA receptor antagonists CPP and Ro 25-6981 on performance of the trial-unique, delayed nonmatching-to-location (TUNL) task in rats

Authors: *D. A. DAVIES, J. L. HURTUBISE, J. G. HOWLAND;
Univ. of Saskatchewan, Saskatoon, SK, Canada

Abstract: The trial-unique, delayed nonmatching-to-location (TUNL) task measures spatial discrimination and working memory in touchscreen-equipped operant chambers. During the task, rats are required to perform delayed non-matching to location trials by touching illuminated regions of a touchscreen. The cognitive load of individual trials can be varied during the task by manipulating the distance between the locations to be discriminated and by increasing the delay between the sample and test phases of a given trial. By varying these parameters, the TUNL task has been proposed to dissociate processes necessary for pattern separation and working memory in a single session. Previous research has linked pattern separation and working memory performance to the activation of NMDA receptors; however, the effects of NMDA receptor antagonists on performance of the TUNL task have not been assessed. Therefore, we tested the effects of the broad spectrum NMDA receptor antagonist 3-(2-Carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP) or the selective GluN2B subunit-containing NMDA receptor antagonist Ro 25-6981 on performance of the TUNL task using a within subjects design in well trained Long Evans rats. After shaping the rats to nose-poke an illuminated stimulus in a touchscreen for food reward, rats were trained in the delayed nonmatching-to-location procedure. A correct selection was rewarded with food whereas an incorrect selection resulted in a time out. After rats consistently achieved 80% correct with large distances between sample and test stimuli (2 s delay), drug treatments were initiated. Injections of CPP (10 mg/kg; i.p.; n = 8) significantly impaired accuracy on trials with a 2 s delay at large distances (vehicle = 90.4% correct; CPP = 74.1%) and small distances (vehicle = 71.0%; CPP = 57.8%). CPP did not significantly impair performance for trials conducted with a 6 s delay (large distance trials, vehicle = 72.0%, CPP = 58.0%; small distance trials, vehicle = 66.0%; CPP = 64.0%). The latency of rats to enter the food port, or respond (correct or incorrect) did not differ among the treatments or delays. Ro 25-6981 (6 mg/kg or 10 mg/kg; i.p.; n = 16) did not affect performance on at either delay or distance. Latency of incorrect responses was significantly decreased following Ro 25-6981 (10 mg/kg). The present results demonstrate a critical role for NMDA receptors in the TUNL task. Future experiments will examine whether NMDA receptors in medial prefrontal cortex and hippocampus make dissociable contributions to the observed impairments in the delay vs. spatial aspects of the task.

Disclosures: **D.A. Davies:** None. **J.L. Hurtubise:** None. **J.G. Howland:** None.

Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.06/CC3

Topic: F.02. Animal Cognition and Behavior

Support: Connecticut College Department of Psychology

Mnemosyne Pharmaceuticals

Title: Comparison of pan- and NR2B-selective NMDA receptor antagonists on locomotor and exploratory behavior, spatial memory acquisition and c-fos expression in rats

Authors: L. M. FLEMING[1], L. S. WATSON[1], M. S. JOHNSON[1], L. R. CORRUBIA[1], N. M. SIGNOR[1], H. G. CHMURA[1], F. S. MENNITI[2], *R. E. GRAHN[1];
[1]Psychology, Connecticut Col., New London, CT; [2]Mnemosyne Pharmaceuticals, Providence, RI

Abstract: The acute and delayed impact of N-methyl-D-aspartate (NMDA) receptor inactivation on cognitive function has been explored recently in the context of animal models of depression and schizophrenia. There are multiple NMDA receptor subtypes that differ in physiology and expression patterns. There is considerable interest in determining the specific functional roles for the different subtypes and, in particular, whether specific subtypes may be targeted for the development of new drugs to treat neuropsychiatric dysfunction. In the present study, locomotor, exploratory, and memory function were examined in male Sprague-Dawley rats 25 min after administration of the NMDA nonselective antagonist ketamine or the selective antagonist for the 2B subunit of the NMDA receptor, traxoprodil mesylate (CP-101,606). In addition, patterns of c-fos expression were examined in the hippocampus, amygdala, bed nucleus of the stria terminalis, the paraventricular nucleus of the hypothalamus and in the medial prefrontal cortex. Our results showed that ketamine reduced locomotion, exploration, and acquisition of spatial memory in the Morris water maze, while CP-101,606-treated rats did not differ from saline-treated rats on these behavioral measures. Ketamine reduced c-fos expression in the mPFC, in CA3 and dentate gyrus subregions of the hippocampus, in the CeA subregion of the amygdala, and in the PVN while CP-101,606 decreased activity only in the prelimbic cortex, the BLA subregion of the amygdala, and in the PVN. These results begin to establish a database correlating unique behavioral effects of NMDA receptor inhibition with neural activity patterns. These relationships will be further explored in subsequent studies.

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Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.07/CC4

Topic: F.02. Animal Cognition and Behavior

Support: NIH R01 grant NS 040723 to Q. Lin

Ronald E. McNair Postbaccalaureate Achievement Program at UT Arlington to R. Stevens

Title: Bumetanide demonstrates amelioration of learning and memory deficits induced by ketamine administration in a neonatal rat model

Authors: *R. STEVENS[1], S. KOKANE[2], B. BUTLER[1], A. WOMACK[2], Q. LIN[2];
[2]Psychology, [1]Univ. of Texas At Arlington, Arlington, TX

Abstract: Ketamine, a non-competitive N-methyl-D-aspartate receptor (NMDAR) antagonist, is widely used as a pediatric anesthetic. Studies reported by our and other groups have shown that neonatal exposure to ketamine causes persistent deficits in learning and memory, and alterations in NMDAR functioning. Additionally, these deficits have been attributed to widespread neuroapoptosis seen in the neonatal brain following ketamine exposure. In adult brains, γ-aminobutyric acid (GABA) neurotransmitter is primarily inhibitory. In contrast, GABA is excitatory upon activation of $GABA_A$ receptors in immature neurons. This is due to greater Na^+-K^+-$2Cl^-$ co-transporter (NKCC1) and weak K^+-Cl^- co-transporter (KCC2) expression in the cell membrane. Thus, bumetanide - an NKCC1 inhibitor - may prevent intracellular Cl^- accumulation rendering GABA inhibitory in immature neurons. We propose that excitatory GABAergic synaptic transmission has a distinct role in mediating ketamine-induced toxicity of neonatal brain neurons, resulting in a significant impact on learning and memory later in life. Therefore, we hypothesized that bumetanide may serve as a neuroprotectant via interfering with this GABA excitatory pathway through inhibiting NKCC1 to minimize ketamine-induced neuroexcitotoxicity. Seven-day-old Sprague-Dawley rats were administered ketamine subcutaneously (S.C., 20 mg/kg, 6X at 2 h intervals); and bumetanide was administered intracerebrally (I.C., 0.02 mg/kg, 3X at 4 h intervals) concurrently with ketamine or vehicle. There were four groups total with various combinations of the aforementioned drug treatments including a vehicle (control) group. Three weeks following treatment, all groups were tested for spatial learning and memory deficits using the Morris water maze (MWM). Animals were trained for 5 days, followed by a probe trial on day 6 to measure short-term spatial memory recall. Impaired learning and memory abilities as compared with the control were indicated by a prolonged latency to find the platform during the 5-day training phase. Prolonged latency was

especially noted in the ketamine treated animals during the training phase, and showed significant deficits in recall of the target platform location during the probe. However, the bumetanide co-treatment group showed a learning rate similar to the control and statistically outperformed the ketamine treated animals. These findings were also confirmed via the probe trial. Thus, these results suggest a new mechanism by which neonatal ketamine-induced learning and memory deficits can be alleviated through reducing hyperactive GABAergic-excitatory neonatal synaptic signaling.

Disclosures: **R. Stevens:** None. **S. Kokane:** None. **B. Butler:** None. **A. Womack:** None. **Q. Lin:** None.

Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.08/CC5

Topic: F.02. Animal Cognition and Behavior

Support: NSERC Grant 400176

NSERC CGS-M

Title: A generalized multisensory binding impairment in ketamine-treated rats: Reversal by α4β2 nicotinic receptor stimulation of the GABAergic system within the orbitofrontal cortex

Authors: *J. M. CLOKE, S. DE LISIO, A. DRUMM, K. BARTON, B. D. WINTERS; Psychology, Univ. of Guelph, Guelph, ON, Canada

Abstract: Schizophrenia is associated with atypical multisensory integration. We have developed a rodent multisensory oddity paradigm (MSO), which enables testing of binding abilities across multiple modalities (tactile-visual & olfactory-visual); in MSO, sets of objects are presented, and normal rats spend significantly more time exploring the one ('odd') object in the set that contains a unique configuration of multisensory features. The present study used the MSO tasks to assess multisensory binding in ketamine-treated rats, a model of schizophrenia. We also investigated the remediating effect of nicotinic acetylcholine receptors (nAChR) and their interaction with GABA systemically and in the orbitofrontal (OFC) and medial prefrontal (mPFC) cortices. Rats were sub-chronically treated with the NMDA receptor antagonist ketamine (30 mg/kg) or saline for 10 consecutive days, after which they were implanted with indwelling cannulas during the 10-day washout period. Ketamine-treated rats were selectively

impaired on the tactile-visual and olfactory-visual MSO tasks; performance on tactile-, visual-, and olfactory-only oddity tasks was spared. Systemic administration of nicotine (0.05, 0.2, & 0.8 mg/kg) reversed the selective MSO impairment in treated rats. The effect of nicotine appeared to be mediated by the α4β2 nAChR, as systemic administration of the α4β2 nAChR agonist ABT-418 (0.06, 0.1, & 0.6 mg/kg) remediated the impairment, but the α7 nAChR agonist GTS-21 (0.3, 1, & 3 mg/kg) did not. Furthermore, intra-OFC, but not intra-mPFC, nicotine (0.5, 1, & 2 μg) reversed the MSO impairment in treated rats. Intra-OFC administration of the α4β2 nAChR agonist ABT-418 (0.3, 1, & 3 μg) also ameliorated the MSO impairment in treated rats; this was blocked by systemic co-administration of the $GABA_A$ antagonist bicuculline (0.5 mg/kg). These results suggest that α4β2 nAChR activation of the GABAergic system within the OFC underlies the remediation of a generalized multisensory binding impairment in ketamine-treated rats. Ongoing studies aim to further elucidate the interaction between nAChRs and GABA in ketamine-treated rats.

Disclosures: J.M. Cloke: None. **S. De Lisio:** None. **A. Drumm:** None. **K. Barton:** None. **B.D. Winters:** None.

Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.09/CC6

Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant DA015351

Title: Synergistic interaction of NMDA and muscarinic receptors in simple response learning

Authors: *I. M. WHITE, Z. ABBOTT, W. WHITE;
Psychology, Morehead State Univ., Morehead, KY

Abstract: Hypofunction of the N-methyl-D-aspartate receptor (NMDAR) and of the muscarinic receptor have been implicated in cognitive deficits and in the pathophysiology of psychiatric disorders. The present study examined NMDAR and muscarinic receptor interaction in simple response learning in rats. Prior to testing, rats were trained on a fixed-ratio 5 (FR5) until their performance reached a behavioral criterion. Systemic injection of an NMDA receptor antagonist, MK-801, and a muscarinic receptor antagonist, scopolamine, disrupted FR5 performance. MK801-induced deficits were partially reversed by SCH23390, a dopamine D1 receptor antagonist, whereas scopolamine-induced deficits were worsened by MK-801, indicating

synergistic interaction of NMDA and muscarinic receptors. Moreover, intra-accumbens infusion of scopolamine did not influence behavior, whereas intraperitoneal administration of scopolamine (0.5mg/kg) increased locomotor activity and impaired simple response learning. Our data suggest that activation of NMDA and muscarinic receptors are required for successful performance in simple response learning and retrieval of learned responding. The nucleus accumbens does not seem likely to be involved in the mechanism that underlies synergistic interaction of NMDA and muscarinic receptors.

Disclosures: I.M. White: None. **Z. Abbott:** None. **W. White:** None.

Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.10/CC7

Topic: F.02. Animal Cognition and Behavior

Title: An intra-amygdala injection of the GABAA agonist, muscimol, prevents fear-induced underestimation of duration

Authors: *T. KAMADA, T. HATA;
Psychology, Doshisha Univ., Kyotanabe, Japan

Abstract: Interval timing, time perception in the seconds-to-minutes range, is known to be altered by emotions such as fear. The neural circuits underlying this effect, however, are not yet well understood. In the present study, we investigated the role of the amygdala in fear-induced alternations in interval timing. Rats were trained on a self-initiated temporal bisection task in which they were required to choose one lever (i.e., the “short lever”) after a 2-s tone and the other lever (i.e., the “long lever”) after a 8-s tone to obtain a food reward. Following sufficient training, the rats were subjected to differential fear conditioning using two tones with different pitches as conditioned stimuli (CSs), i.e., one pitch (CS+) was paired with an electric foot shock (unconditioned stimulus; US), whereas the other (CS-) was not. The rats were infused with either vehicle (artificial cerebrospinal fluid; aCSF) or the gamma-aminobutyric acid (GABA)A agonist, muscimol (4.4 nmol), into the bilateral amygdala before the fear conditioning session, and then tested on the bisection task using the CS+ and CS- as to-be-timed stimuli. In vehicle-infused rats, the CS+ induced a rightward shift in the psychophysical functions and an increase in the point of subjective equality (PSE) without a change in a difference limen (DL) or the range of the psychophysical functions compared with the CS-, suggesting that conditioned fear induces underestimation of duration. Interestingly, this result is in contrast to human studies, which

report fear-induced overestimation of duration. During the presentation of a to-be-timed stimulus, well-trained rats exhibit a stable temporal behavior, i.e., they initially stay in front of the short lever, wait a period of time, and then shift toward and remain in front of the long lever. So, we also conducted a single trial analysis using the time of arrival at the long lever (i.e., the "arrival latency") to investigate the dynamics of the effect of conditioned fear within a session. In vehicle-infused rats, the arrival latency in the CS+ increased in the early phase of the test session but gradually decreased as the test session progressed, suggesting that the effect of conditioned fear is extinguished by repeated presentation of the CS+. However, muscimol-infused rats in which fear was presumably not conditioned did not show a change in PSE and arrival latency in the CS+ throughout the test session. Taken together, these results suggest that fear-induced underestimation of duration is mediated by the amygdala.

Disclosures: T. Kamada: None. **T. Hata:** None.

Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.11/CC8

Topic: F.02. Animal Cognition and Behavior

Support: The current study and presentation are supported by H. Lundbeck A/S and Otsuka Pharmaceutical Development & Commercialization

Title: Distribution of 5-HT_6 receptor mRNA in the rat brain and effects of the 5-HT_6 antagonist idalopirdine on extracellular levels of neurotransmitters and neuronal oscillations

Authors: *A. MORK[1], G. SMAGIN[2], L. HELBOE[1], K. F. HERRIK[1], M. A. FORASTER[1], D. SONG[2], D. P. BUDAC[2], H. ARMANDI[1], I. E. M. DE JONG[1];
[1]H. Lundbeck A/S, Copenhagen-Valby, Denmark; [2]Lundbeck Res. USA, New Jersey, NY

Abstract: The 5-HT_6 receptor (R) is almost exclusively expressed in the CNS. Combining a 5-HT_6 R antagonist with an acetylcholinesterase inhibitor (AChEI) represents a promising new approach for symptomatic treatment of Alzheimer's disease. A recent phase 2 trial showed that the selective 5-HT_6 R antagonist idalopirdine (Lu AE58054) improved cognitive performance in patients with moderate Alzheimer's disease on stable donepezil treatment. In the present study we examined cell type specific expression of 5-HT_6 R mRNA and effects of idalopirdine on levels of neurotransmitters and local field potentials in the rat brain. QuantiGene® ViewRNA platform from Affymetrix was applied to perform *in situ* hybridization in brain sections of male

Sprague Dawley rats. Following total mapping 5-HT_6 R mRNA visualization was combined with probes for a range of neurotransmitters or interneuronal markers. Extracellular levels of neurotransmitters in the medial prefrontal cortex (mPFC) of freely moving male Sprague Dawley rats were measured by microdialysis; samples were analyzed by HPLC with electrochemical detection or LC/MS/MS.In anesthetized male Sprague Dawley rats local field potentials were recorded with tungsten electrodes in the mPFC, while brainstem (nucleus pontis oralis) electrical stimulation was applied (0.3ms square pulses, 6s, 250Hz) every 100s. Recordings were transformed using a modified continuous wavelet transform to yield the power of oscillatory activity.The majority of 5-HT_6 R expressing neurons were glutamatergic or GABAergic principal neurons. A subset of GABAergic interneurons expressed 5-HT_6 R mRNA, the majority of which belonged to the 5-HT_{3a} R expressing subpopulation. Subpopulations of calbindin- and calretinin-positive GABAergic interneurons also expressed 5-HT_6 R mRNA. Administration of idalopirdine alone (10 mg/kg po) increased extracellular levels of monoamines and glutamate in the mPFC but did not affect acetylcholine (ACh) levels. The AChEI donepezil at 1.3 mg/kg (sc) increased the ACh levels and co-administration of idalopirdine and donepezil seemed to further increase the cortical ACh levels compared to donepezil alone. Pretreatment with idalopirdine at 2 mg/kg (iv) potentiated the effect of donepezil at 0.3 mg/kg (iv) on gamma oscillations in the mPFC.The localization study suggests that the 5-HT_6 R is positioned to regulate the balance between excitatory and inhibitory signaling. The enhancements by idalopirdine of levels of several neurotransmitters and the potentiation of the effects of donepezil may contribute to the idalopirdine-improved cognitive performance of patients on stable donepezil treatment.

Disclosures: **A. Mork:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S. **G. Smagin:** A. Employment/Salary (full or part-time):; H. Lundbeck USA. **L. Helboe:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S. **K.F. Herrik:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S. **M.A. Foraster:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S. **D. Song:** A. Employment/Salary (full or part-time):; H. Lundbeck USA. **D.P. Budac:** A. Employment/Salary (full or part-time):; H. Lundbeck USA. **H. Armandi:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S. **I.E.M. de Jong:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S.

Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.12/CC9

Topic: F.02. Animal Cognition and Behavior

Support: Janssen research grant

Title: Serotonin (5-HT)7 receptor antagonists reduces cortical and striatal glutamate efflux and reverses cognitive impairment induced by phencyclidine

Authors: *M. HUANG, L. RAJAGOPAL, S. KWON, E. E. MICHAEL, H. Y. MELTZER; Psychiatry and Behavior Sci., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: Background: There is extensive preclinical evidence that serotonin (5-HT)7 receptor blockade is a promising target for treatment of cognitive impairment and major depression. However, there is also evidence that 5-HT7 agonists have pro-cognitive properties. We have reported that atypical antipsychotics (APDs), e.g. lurasidone, clozapine, risperidone, and amisulpride, which are potent 5-HT7 receptor antagonists, in a 5-HT7 dependent manner, can prevent the cognitive impairment induced by sub-chronic phencyclidine (scPCP), a widely studied rodent model of cognitive impairment of schizophrenia. All have been reported to improve some domains of cognition in schizophrenia patients. Atypical APDs have been shown to suppress acute effects of PCP to increase cortical glutamate (Glu) and 5-HT efflux, possibly contributing to their pro-cognitive actions. Methods: We have now studied the ability of SB 269970, and a novel 5-HT7 antagonist, JNJ 18038683 ((3-(4-chlorophenyl)-1,4,5,6,7,8-hexahydro-1-(phenylmethyl)pyrazolo[3,4-d]azepine 2-hydroxy-1,2,3-propanetricarboxylate)) to reverse the deficit in novel object recognition (NOR), a hippocampus and prefrontal cortex dependent task, induced by scPCP, as well as on the PCP-induced efflux of Glu, 5-HT and other neurotransmitters, in mouse medial prefrontal cortex (mPFC) and dorsal striatum (dSTR). Results: Both SB 269970 (1 mg/kg, i.p.) and JNJ18038683 (1 mg/kg) reversed the scPCP-induced deficit in NOR. Data on the ability of the selective 5-HT7 antagonists to affect NOR in normal animals and to block acute PCP-induced impairment in NOR will be presented during the meeting. SB 269970 (3 mg/kg) and JNJ 18038683 (3 mg/kg), given alone, significantly, increased Glu and 5-HT efflux in mPFC and dSTR. Both increased dopamine (DA) efflux in the mPFC, but only SB 269970 increased DA in the dSTR. SB 269970 and JNJ 18038683 increased cortical but not dSTR 5-HT efflux. When given 30 min before PCP (10 mg/kg), both compounds significantly suppressed the PCP-induced Glu efflux in both regions. Moreover, JNJ 18038683 suppressed norepinephrine efflux in both regions; SB 269970 did so only in dSTR. Neither compound affected PCP's ability to enhance acetylcholine, 5-HT and DA efflux in either region. Conclusion and Discussion: These results provide additional support for 5-HT7R antagonism as a promising target for the treatment of cognitive impairment, possibly via effects on glutamatergic, serotonergic, dopaminergic and noradrenergic neurotransmission, all of which participate in memory formation and retrieval.

Disclosures: M. Huang: None. **L. Rajagopal:** None. **S. Kwon:** None. **E.E. Michael:** None. **H.Y. Meltzer:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report

that research relationship even if those funds come to an institution.; Research grant. F. Consulting Fees (e.g., advisory boards); Consultant.

Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.13/CC10

Topic: F.02. Animal Cognition and Behavior

Title: The selective serotonin (5-HT)7R antagonist, SB269970 prevents and reverses declarative memory deficits produced by sub-chronic phencyclidine in mice and normalizes hippocampal long-term potentiation

Authors: *L. RAJAGOPAL[1], H. FERNANDES[2], M. HUANG[3], A. CONTRACTOR[4], H. Y. MELTZER[5];
[1]Psychiatry and Behavioral Sci., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL; [2]Physiol., Norhtwestern Univ., Chicago, IL; [3]Psychiatry and Behavioral Sci., Northwestern Univ., chicago, IL; [4]Physiol., [5]Psychiatry and Behavioral Sci., Northwestern Univ., Chicago, IL

Abstract: Introduction: The selective serotonin (5-HT)7R antagonist, SB269970 (SB269), as well as atypical antipsychotic drugs, e.g. lurasidone and amisulpride with high 5-HT7R affinity, have been shown to ameliorate sub-chronic (sc) phencyclidine (PCP)-induced cognitive deficits in rats in a 5-HT7R dependent manner. The scN-methyl-D-aspartate receptor (NMDAR) antagonist, PCP, produces enduring deficits in novel object recognition (NOR), an analog of human declarative memory. We have recently shown that scPCP causes long-lasting metaplastic changes in the inhibitory principal neurons in the hippocampus (HIP) that results in impaired long-term potentiation (LTP). The present study investigated the ability of acute or sc SB269 to reverse or prevent scPCP-induced NOR deficits in C57BL/6J mice and to ameliorate the impairment in LTP in slices from the HIP-CA1 region in scPCP-treated mice. Methods: Four cohorts of male C57BL/6J mice (N=8-10 per group) were used. The NOR and electrophysiology methods are described elsewhere (Horiguchi et al., 2012, Nomura et al., 2015). The same drug treatment protocol was carried out for both behavioral and electrophysiological studies (ES). For ES, the animals were sacrificed for HIP brain slice recordings (BSRs) 30 minutes after SB26 injection in acute studies and on day 15 for prevention studies (PS). In the acute reversal study, animals were given saline, scPCP (10 mg/kg; b.i.d. for 7 days, 7 days washout), or scPCP+SB269 (0.3, 0.5, or 1 mg/kg) 30 min prior to NOR. In PS, the animals were given scSB269 (4 mg/kg; i.p. b.i.d, 7 days) prior to PCP on days 1-7, 7 days washout. NOR testing was

done on day 15. In enduring reversal study (ERS), animals were given scPCP on days 1-7; 7 days washout. scSB269 was given on days 15-21 and NOR began on day 22. Results: In the acute reversal study scPCP-induced NOR deficit was significantly reversed by SB269, 1.0, but not 0.3 or 0.5 mg/kg ($P<0.001$). scPCP impaired LTP at HIP-CA1 region was restored in acute SB269 mice ($P<0.001$). In the PS, scSB269, 4 mg/kg, prevented scPCP-induced NOR deficits for at least 8 weeks ($P<0.05$-$P<0.001$) and prevented scPCP-induced impairment in LTP at HIP-CA1 region ($P<0.001$). In the ERS, scSB269, 4 mg/kg reversed scPCP-induced NOR deficit for 3 weeks ($P<0.05$-$P<0.01$), after which the deficit returned. Conclusion: The results reported here provide important new evidence for the role of 5-HT7R blockade to ameliorate NOR deficit in scPCP-treated mice. 5-HT7R blockade can prevent the development of PCP-induced cognitive deficit and can acutely reverse it once established. 5-HT7R blockade can also enable the circuitry that can restore NOR for a prolonged period of treatment.

Disclosures: L. Rajagopal: None. **H. Fernandes:** None. **M. Huang:** None. **A. Contractor:** None. **H.Y. Meltzer:** None.

Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.14/CC11

Topic: F.02. Animal Cognition and Behavior

Support: FAPESP 2013/20378-8

Title: Differential hippocampal expression of 5htr1a in conditioned suppression of fear memory

Authors: C. R. ZAMBERLAM, L. MORAES, J. M. CERUTTI, *S. M. CERUTTI;
Univ. Federal De Sao Paulo, Sao Paulo, Brazil

Abstract: In this study, we investigated whether the expression of genes that were previously associated with acquisition of fear memory or anxiety and that are modulated following short-term standardized extract of Ginkgo biloba (EGb) treatment are also regulated following acquisition or extinction of CER in the DH. The 5-HT1A receptor (5-hydroxytryptamine receptor subtype 1A) is differently expressed in DH of rodents and humans and it was associated with both short and longterm memory. Male adult Wistar rats were treated with one dose before fear conditioning of EGb (250 mg.Kg-1, 500 mg.Kg-1 and 1000 mg.Kg-1),vehicle (Tween® and Saline), agonists (10.0mg.Kg-1 Buspirone) or antagonists (0.3 mg.Kg-1 (S)-WAY100135) of the 5-HT1AR or antagonists+EGb ((S)-WAY+EGb) (n=10/group). Rats were fear conditioned in a

lick-operandum chamber. The behavioral procedure was conducted for eight or ten days, according experimental design to access acquisition or extinction of conditioned emotional response (CER). One half of the rats (n=5/group) were decapitated 3 hours after acquisition test (8th Day). Other half (n=5/group) was submitted to extinction training (9th day) and extinction retention test (10th day). Three hours after retention test Test (8 th day) extinction retention text (10th day) the rats were decapitated and the DH was extracted within 40-60 s with a magnifying glass, immediately frozen on dry ice, and maintained at -80oC until gene expression analysis. The analysis of gene expression of 5htr1a receptors in the DH was performed by quantitative polymerase chain reaction (qPCR). RNA samples had been previously extracted and the cDNA obtained for the quantitative analysis. Group treated with 500mg.Kg-1 EGb resulted in the overexpression of 5htr1a (Re = relative expression, Re=5,36) in the extinction of fear conditioning when compared with Tween group (Re=1,0;P<0.05) and manipulated (Re= 0,35: P<0.001). 5htr1a was increased in the DH to groups treated with ((S)-WAY before EGb, at three doses, (250 mg.Kg-1; Re=89,92; 500 mg.Kg-1 Re=56,29; 1000 mg.Kg-1;Re=38,96, p<0,0001), when compared to the control group (Sway; Re=0,94; Tween Re=1,10; p<0,0001). Further, comparative analysis among groups treated with EGb and (S)-WAY+EGb, showed that treated with antagonist before EGb resulted in overexpression of 5htr1a, at three doses, according to ANOVA followed by a Bonferroni post hoc test. Altogether, our findings contribute to the view that EGb modulated the serotoninergic neurotransmission in DH, which seems to be involved in the extinction of conditioned fear of dose-dependent manner.

Disclosures: C.R. Zamberlam: None. **L. Moraes:** None. **J.M. Cerutti:** None. **S.M. Cerutti:** None.

Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.15/CC12

Topic: F.02. Animal Cognition and Behavior

Title: Brain functions and dysfunctions: memory, serotonin and neural markers

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Abstract: Diverse neuropsychiatric disorders present dysfunctional memory and no effective treatment exits for them, likely related to the absence of neural markers associated to memory. Neurotransmitter systems and signaling pathways have been implicated in memory formation,

dysfunctional memory and forgetting; however, their role is poorly understood. Herein, neural markers and cerebral functions and dysfunctions are revised. To our knowledge no previous systematic works have been published addressing these issues. Hoping offering new insights, examples illustrating the interaction among behavioral tasks, control groups and molecular changes and/or pharmacological effects are briefly mentioned. Actually, serotonin has pharmacological tools and well characterized downstream signaling in mammals' species, and serotonin is one of the best characterized neurotransmitter, hence the role of this monoamine in memory is the focus but other neurotransmission systems and downstream signaling are discussed. Promissory and abundant findings exist supporting the use of neural markers for cerebral functions and dysfunctions. Certainly, at least 5-HT1A, 5-HT4, 5-HT6 and 5-HT7 receptors as well as SERT (serotonin transporter) seem to be useful neural markers and therapeutic targets. Likewise, hypothesis and theories might provide appropriate limits and perspectives of evidence. If the mentioned evidence is replicated, then the translatability of diverse approaches of preclinical and clinical studies to neural changes might be confirmed

Disclosures: **A. Meneses:** None.

Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.16/CC13

Topic: F.02. Animal Cognition and Behavior

Title: SUVN-I1411030, muscarinic (M1) acetylcholine receptor- positive allosteric modulator (PAM) for the treatment of age associated cognitive impairment

Authors: ***R. ABRAHAM**[1], R. SUBRAMANIAN[2], R. BABU MEDAPATI[3], R. VENKATESHWARLU[3], S. YATHAVAKILLA[3], S. IRUPANNANAVAR[4], R. CHOWDARY[4], V. UTHUKAM[4], B. DEVARAPALLI[4], S. PANDEY[5], A. SHINDE[6], V. TIRIVEEDHI[6], V. REBALLI[6], R. NIROGI[1];
[2]in-vitro biology, [3]In-vivo Pharmacol., [4]ADME, [5]Toxicology, [6]Chem., [1]Suven Life Sci., Hyderabad, India

Abstract: Alzheimer's disease (AD) and dementia are the widely known causes for the loss of memory in the elderly people. Currently, there are only symptomatic treatments available for the above mentioned conditions. M1 agonist compounds evaluated in past though showed cognitive improvement, had limited clinical utility due to cholinergic side effects hypothesized to result from non -selective action on M2 to M5 subtypes. Due to the conservative nature of the

orthosteric M1 site, we explored the possibility of identifying the positive allosteric modulators of M1 receptor. SUVN-I1411030, a hydrochloride salt compound is one of our lead molecules. SUVN-I1411030 caused a leftward shift of acetycholine when tested in the reporter gene assay method. SUVN-I1411030 was found to be orally bioavailable (60%) with an adequate brain penetration index (~0.46) in rats. SUVN-I1411030 reversed the time and scopolamine induced memory deficit in rat. Sub efficacious dose of SUVN-I1411030 in combination with donepezil showed procognitive activity. SUVN-I1411030 also promotes non- amyloidogenic APP processing in rats. SUVN-I1411030 did not enhance salivation when administered along with acetylcholine esterase inhibitors. SUVN-I1411030 was found to be safe when tested in hERG Patch clamp assay for assessing cardiotoxicity (IC50> 10 μM). SUVN-I1411030 was found to have a high margin of safety in acute toxicity studies. SUVN-I1411030 was found to have > 25 mg/mL solubility. Further detailed profiling of this compound is currently ongoing

Disclosures: R. Abraham: A. Employment/Salary (full or part-time):; Suven Life Sciences. **R. Subramanian:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **R. Babu Medapati:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **R. Venkateshwarlu:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **S. Yathavakilla:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **S. Irupannanavar:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **R. Chowdary:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **V. Uthukam:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **B. Devarapalli:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **S. Pandey:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **A. Shinde:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **V. Tiriveedhi:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **V. Reballi:** A. Employment/Salary (full or part-time):; Suven Life Sciences. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences.

Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.17/CC14

Topic: F.02. Animal Cognition and Behavior

Title: Improvement in translatable touchscreen tests of memory and attention with an M1 muscarinic positive allosteric modulator in rhesus monkeys

Authors: *H. S. LANGE[1], C. E. CANNON[2], J. DROTT[1], S. D. KUDUK[2], J. M. USLANER[1]; [1]Pharmacol., [2]Merck Res. Labs., West Point, PA

Abstract: Improved treatment for Alzheimer's disease (AD) is a significant unmet medical need given the continued rise in the number of patients and the substantial economic burden that the disease creates. The current standards of care, which are primarily acetylcholinesterase inhibitors (AChEIs), are hindered by gastrointestinal (GI) side effects due to their nonselective activation of muscarinic and nicotinic receptors. Recently, the M1 positive allosteric modulator PQCA (1-((4-cyano-4-(pyridine-2-yl)piperidin-1-yl)methyl-4-oxo-4 H-quinolizine-3-carboxylic acid) has been demonstrated to improve cognition in a variety of rodent and non-human primate cognition models without producing significant GI side effects. Here we describe the effect of PQCA and the AChEI donepezil on two clinically relevant and highly translatable touchscreen cognition tasks in NHPs, paired-associates learning (PAL) and the continuous performance task (CPT). Blockade of muscarinic signaling by scopolamine produced significant impairments in both PAL and CPT. PQCA and donepezil attenuated the scopolamine deficits in both tasks, and the action of these two compounds was similar in magnitude. In addition, the combination of subeffective doses of PQCA and donepezil enhanced PAL performance. These results suggest that M1 positive allosteric modulators have potential to reduce the cognitive deficits associated with Alzheimer's disease either as monotherapy or as an add-on to current standards of care.

Disclosures: H.S. Lange: A. Employment/Salary (full or part-time):; Merck Research Laboratories. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Merck Research Laboratories. **C.E. Cannon:** A. Employment/Salary (full or part-time):; Merck Research Laboratories. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Merck Research Laboratories. **J. Drott:** A. Employment/Salary (full or part-time):; Merck Research Laboratories. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Merck Research Laboratories. **S.D. Kuduk:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Merck Research Laboratories. **J.M. Uslaner:** A. Employment/Salary (full or part-time):; Merck Research Laboratories. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Merck Research Laboratories.

Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.18/CC15

Topic: F.02. Animal Cognition and Behavior

Support: University of Houston-Clear Lake Faculty Research Support Fund

Title: Scopolamine creates dose-dependent memory rather than sensorimotor impairment of latent learning in the water maze

Authors: *J. J. IZYGON, D. M. NGHIEM, M. M. HENCEROTH-CHOMIAK, D. J. MCGHIEY, R. TIJERINAR, M. F. MERIANO, P. GOYARZU, J. L. HAVENS, D. H. MALIN; HSH, Univ. of Houston Clear Lake, Houston, TX

Abstract: Most water maze studies model trial and error learning, as opposed to spatial learning by mere observation. Previous research in our laboratory, indicates that, with a revised procedure, highly efficient latent learning can be accomplished through direct placement of rats on the submerged water maze platform so that they can observe its location. This ability was almost entirely abolished by muscarinic cholinergic blockade with scopolamine thirty minutes before platform placement. A dose-dependence experiment compared the effects of i.p. injection of 1 mg/kg or 0.6 mg/kg of scopolamine HBr or saline alone. One-way ANOVA indicated a highly significant scopolamine dose effect on latency to swim back to the platform 5 minutes later, $p = .002$, and on accuracy of the rat's path to the platform relative to a direct route, $p = .001$. There was a significant negative linear trend of latency as a function of dose, $p = .05$ and a significant positive linear trend of accuracy as a function of dose, $p = .029$. To evaluate whether scopolamine's negative effects on performance were due to sensorimotor impairment, rats were tested for latency and accuracy of swimming to a non-submerged visible platform complete with a small flag. This eliminated any reliance on spatial memory. The subjects were 6 Long-Evans rats, who received the higher 1.0 mg/kg dose of scopolamine HBr on two days, alternating with two days receiving saline. It was found that rats performed almost identically after scopolamine or saline injection. They reached the visible platform in an average of 6.47 ± 1.61 (M ± SEM) seconds on days with saline injection, versus 5.74 ± 0.73 seconds on days with scopolamine injection. This difference was not significant, $p = .62$. After saline injection, they averaged $70.6\% \pm 6.5\%$ accuracy of swim trajectory as compared with $67.2\% \pm 5.4\%$ accuracy after scopolamine injection. This difference was also not significant, $p = .52$. These results suggests that muscarinic cholinergic blockade affects water maze latent learning, not through sensorimotor impairment, but through interference with spatial memory processes.

Disclosures: J.J. Izygon: None. **D.M. Nghiem:** None. **M.M. Henceroth-Chomiak:** None. **D.J. McGhiey:** None. **R. Tijerinar:** None. **M.F. Meriano:** None. **P. Goyarzu:** None. **J.L. Havens:** None. **D.H. Malin:** None.

Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.19/CC16

Topic: F.02. Animal Cognition and Behavior

Title: Memory reconsolidation and scopolamine-induced amnesia modulated by guineensine in BALB/c mice

Authors: *I. C. REYNOSO-MORENO[1], A. N. ROSAS-ESCAREÑO[1], C. R. GUZMAN-PEREZ[1], M. E. FLORES-SOTO[2], J. M. VIVEROS-PAREDES[1];
[1]Univ. De Guadalajara (CUCEI), Guadalajara, Mexico; [2]Ctr. de Investigacion Biomedica de Occidente, Guadalajara, Mexico

Abstract: The high concentration of cannabinoid receptor type 1 (CB1) in the hippocampus, suggests that endocannabinoid system may play a role in learning and memory processes. Studies demonstrate that is critical for the encoding of emotional memory and for the extinction of fear-related memories. Also, studies have shown that the administration of CB1 agonists impairs memory and antagonists may improve. On the other hand, guineensine (present in *Piper nigrum)* was identified as inhibitor for endocannabinoid reuptake. In the cannabinoid tetrad test, guineensine dose-dependently induced cannabimimetic effects; shown strong catalepsy, hypothermia, reduced locomotion and analgesia. Therefore, the aim of this work was study if guineensine is able to modify acquisition or reconsolidation in the inhibitory avoidance test (hippocampal-dependent and fear-related memory paradigm). Also, we used scopolamine-induced amnesia for know if guineensine abolishes their effect. Due to that catalepsy and analgesia could interfere in mice performance, we used doses that not have this effects. The inhibitory avoidance test was carried in a box with light (500 lux), and dark compartments of equal size (20 x 20 cm). BALB/c mice (male, 22-25 g) were placed in the light side. For conditioning, when the mouse crossed over the dark side, it received a footshock (0.08 mA) for 10 s. For reconsolidation (48 h after), if crossed at the dark side no footshock was given. The retention trial was 24 h later. The crossover latency was recorded. Scopolamine (1 mg/kg, i.p.) or vehicle was administered 1 h before of acquisition trial, and guineensine (0.25 or 2.50 mg/kg, i.p.) or vehicle was administered 20 min before of reconsolidation trial. In resume, guineensine at 0.25 mg/kg decreased the crossover latency in reconsolidation and retention trial ($p<0.001$), therefore impairs the conditioning. At high dose (2.50 mg/kg), guineensine decreased the latency in retention trial ($p<0.001$), therefore impairs the reconsolidation. In the groups with scopolamine-induced amnesia, low dose of guineensine not have effect; however, at high dose, guineensine increased the crossover latency in reconsolidation ($p<0.001$) and retention trial ($p<0.05$), therefore abolishes the effect of scopolamine; this result must be better assayed

because anandamide could binding to nicotine receptors. In general, guineensine impairs acquisition memory process, in agree with other studies showing enhance anandamide levels and learning impair. It important to mention that studies with other inhibitor of uptake have presented improve of memory extinction; therefore, guineensine must be test in these assay.

Disclosures: **I.C. Reynoso-Moreno:** None. **A.N. Rosas-Escareño:** None. **C.R. Guzman-Perez:** None. **M.E. Flores-Soto:** None. **J.M. Viveros-Paredes:** None.

Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.20/CC17

Topic: F.02. Animal Cognition and Behavior

Title: Evaluating putative deficit models in a hippocampal-dependent assay sensitive to task manipulations, aging and pharmacology

Authors: *R. GRAF[1], J. L. LONGO[2], Z. HUGHES[1];
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Abstract: Cognitive dysfunction is a key symptom of CNS disorders including schizophrenia and Alzheimer's disease. Currently, there are limited treatment options available that effectively improve cognitive deficits. Our research aimed to evaluate a rodent testing paradigm sensitive to cognitive disruptions as well as for detecting agents which restore cognitive function. Since patients with schizophrenia and Alzheimer's disease exhibit deficits in pattern separation, we established an assay to assess spatial learning, or pattern separation, in mice using touchscreen technology. The Location Discrimination Reversal (LD) task is a reward-based operant behavioral test that relies on the hippocampus, specifically the dentate gyrus to assess location memory by simultaneously displaying two identical stimuli in separate locations on a screen. The mice were trained to discriminate between the two illuminated images by pairing the correct response with a food reward; once learnt, the rule was then reversed. Three ways of impairing performance were evaluated. The first method involved reducing the discrimination index by decreasing the separation between the stimuli. There was separation dependent performance impairment as stimuli were presented closer together from intermediate (baseline) to minimum (hard) to adjacent (very hard) separations. The second method investigated whether the task was sensitive to age related cognitive decline by beginning training of mice when they were 11 months old. Compared to a younger cohort who began training in the same task at 3-4 months of

age, this cohort of aged mice required significantly more trials to reach criterion ($p<0.0001$). The final type of manipulation to cause a cognitive deficit was pharmacological intervention in adult mice. Mice were dosed with the muscarinic antagonist scopolamine (0.32 and 0.56 mg/kg, SC) or the NMDA antagonist, MK-801 (0.056 mg/kg, SC). Administration of scopolamine or MK-801 impaired performance which was evident in the exacerbation of the separation dependent deficit. In summary, here we demonstrated that performance in the LD task is sensitive to manipulations of task difficulty, age and pharmacological disruption. Work is ongoing to determine whether the cognitive deficits described in the LD task can be attenuated by compounds with cognitive enhancing properties.

Disclosures: R. Graf: None. **J.L. Longo:** None. **Z. Hughes:** None.

Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.21/CC18

Topic: F.02. Animal Cognition and Behavior

Title: Blocking α7 nicotinic acetylcholine receptors improves specifically memory acquisition

Authors: *N. P. VAN GOETHEM[1], E. FEDELE[2], D. PUZZO[3], C. REBOSIO[2], W. GULISANO[3], A. PALMERI[3], L. P. WENNOGLE[4], Y. PENG[4], H. W. M. STEINBUSCH[1], J. PRICKAERTS[1];
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Abstract: α7 nicotinic acetylcholine receptors (α7nAChRs) are ligand-gated ion channels expressed primarily in the brain. These receptors have been implicated in modulating cognitive functions like episodic memory and attention. Hence, α7nAChR agonists/modulators may be attractive drug candidates to improve cognition in Alzheimer's disease (AD) and schizophrenia. In the current study, the cognition enhancing properties of low dose administration of selective α7nAChR antagonists were investigated in rats as low doses of methyllycaconitine (MLA) have sporadically been reported to improve cognition in animals. Memory acquisition and consolidation processes were assessed separately with the object recognition task (ORT). The compounds used for these studies were MLA and Compound 7i. Interestingly, it was found that low doses of MLA and Compound 7i improved the acquisition, but not the consolidation processes of object recognition memory at a 24 h retention interval. Conversely, higher doses

impaired the memory performance at a shorter 1 h retention interval. In addition, the same compounds were studied in a model of neuronal plasticity, long-term potentiation (LTP). It was demonstrated that pre-tetanus low-dose administration of MLA or Compound 7i produced a longer lasting potentiation, whereas post-tetanus administration had no effect. Microdialysis studies showed that MLA administration substantially increased hippocampal glutamate efflux which has been found to be related to object memory processes. In summary, blocking α7nAChRs with low doses of selective antagonists improves specifically the memory acquisition process. While the main focus of the α7nAChR as a target for cognition enhancement lies on agonists and positive modulators, antagonism of these receptors at low doses might also prove to be a valuable tool for cognition enhancement in AD or schizophrenia.

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Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.22/CC19

Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant DA029292

Title: Effects of amnestic drugs on memory capacity in the rodent odor span task

Authors: M. MATHEWS, D. PANOZ-BROWN, A. PRICHARD, S. HESS, K. GOBENCIONG, J. COFFMAN, *J. GALIZIO;
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Abstract: Ketamine (NMDA antagonist), scopolamine (anticholinergic), zolpidem and flunitrazepam (positive allosteric $GABA_A$ modulators) have been associated with memory impairments in a variety of animal models. The present study used the odor span task to assess drug-induced deficits in working memory capacity in rats. The odor span task uses an incrementing non-match to sample procedure in which responses to a new olfactory stimulus result in reinforcement on each trial, while responses to previously presented stimuli are not reinforced. Responses were made by removing scented lids from cups presented in the arena. On each trial a novel stimulus was added, progressively incrementing the number of odors to remember (memory load). Six trials of a simple olfactory discrimination task, as a performance

control, were interspersed in each session to assess drug-induced impairments unrelated to working memory. dependent measures included number of consecutive correct responses prior to the first error (span), longest run of correct responses and overall accuracy. Rats were trained to a stability criterion prior to drug administration. Acute administration of all four compounds produced a dose dependent reduction in span, longest run and overall accuracy, but for ketamine, scopolamine, and zolpidem, this generally occurred only at doses in which performance on the simple discrimination control was also impaired. In contrast, acute flunitrazepam administration produced a dose dependent decrease in span, longest run and overall accuracy at doses that had no effect on the simple discrimination control. These results indicate that not all amnestic drugs produce selective deficits in the odor span task which may have a bearing on understanding the neurochemical basis of memory capacity.

Disclosures: **M. Mathews:** None. **D. Panoz-Brown:** None. **A. Prichard:** None. **S. Hess:** None. **K. Gobenciong:** None. **J. Coffman:** None. **J. Galizio:** None.

Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.23/CC20

Topic: F.02. Animal Cognition and Behavior

Support: ES07051

Title: Methamphetamine-induced changes to monoamine neurotransmission and allocentric learning and memory in barren-housed adult rats

Authors: ***A. GUTIERREZ**[1,3], S. A. JABLONSKI[2], R. M. AMOS-KROOHS[4], A. A. BRAUN[2], M. T. WILLIAMS[2,3], C. V. VORHEES[2,3];
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Abstract: Dopamine (DA) modulates brain regions known to be involved in learning and memory (L&M). The effects of methamphetamine (METH) on the dopaminergic system have been well characterized although the effects on allocentric spatial L&M have been unclear. Chronic stress can enhance or decrease cognitive performance depending on the intensity of the stressor. The current study investigated the effects of barren housing (BAR) on brain monoamines and L&M in METH-treated adult rats. Adult Sprague-Dawley males were housed

in standard housing (with bedding) or in BAR housing, consisting of a cage with no bedding and only a single paper towel. The animals continued to be housed this way for 3 weeks. At the 3-week point, blood was collected and the animals were treated with 10 mg/kg METH, 4 times at 2 h intervals. Temperatures were monitored throughout METH dosing. The animals were then allowed another 2 weeks to recover. At 2 weeks, one group of animals underwent behavioral testing in a 244 cm Morris water maze (MWM), while a second group had blood and brain tissue collected. Behavioral testing consisted of a day of straight channel, followed by an acquisition, reversal, shift, and cued phase. All phases, with the exception of the cued phase, consisted of 6 days of learning trials, and a one-day memory probe trial. The cued phase totaled 2 days. The second group of animals were sacrificed 2 weeks after METH treatment, blood was collected, and dorsal striatum (DS), nucleus accumbens (NAcc), and hippocampus (HIP) were collected. Monoamine levels were analyzed by HPLC-ECD. Glial fibrillary acidic protein (GFAP) expression was analyzed by western blotting. METH significantly increased temperatures during dosing. METH treatment produced behavioral deficits during the learning trials of all 3 phases. BAR animals performed better than standard-housed animals during the acquisition, but not reversal or shift phase. Reversal and shift, but not acquisition, probe trials were negatively affected by METH treatment. METH treatment significantly decreased DA and its metabolite, 3,4-dihydroxyphenylacetic acid (DOPAC) in the DS. A cage x drug interaction was detected for DOPAC levels in the DS (BAR increased DOPAC in saline animals). METH treatment also decreased levels of serotonin (5-HT) and its metabolite, 5-Hydroxyindoleacetic acid (5-HIAA) in the DS. Increases in expression of GFAP within the DS and the NAcc, but not the HIP, were detected. A cage x drug interaction was detected in the NAcc where BAR housing afforded protection against increased expression of GFAP in METH-treated animals. CORT levels at both time points and monoamine levels in the NAcc and HIP are currently being analyzed.

Disclosures: **A. Gutierrez:** None. **S.A. Jablonski:** None. **R.M. Amos-Kroohs:** None. **A.A. Braun:** None. **M.T. Williams:** None. **C.V. Vorhees:** None.

Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.24/CC21

Topic: F.02. Animal Cognition and Behavior

Support: Grant IN224314 from DGAPA-UNAM to OPG

PosDoc DGAPA-UNAM to BAMC

Title: GPR55 modulates procedural memory

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Abstract: GPR55 receptor is highly activated by several endocannabinoids. This receptor interacts functionally with CB1/CB2 receptors in different tissues; however, its functions in the Central Nervous System are practically unknown. Although GPR55 has been involved in bone dynamics, pain perception, vasomotor regulation and locomotor coordination, no systematic studies have analyzed its potential role in cognitive function regulation. As this receptor is widely expressed in the striatum, a brain structure that participates in procedural memory regulation, our aim was to analyze the role of striatal GPR55 on this type of memory. Therefore, we set up pharmacological experiments to evaluate the effect of striatal GPR55 stimulation/blockade on rat performance in a T-maze task. Wistar rats were trained to learn the strategy-1 (S1; reinforcer was in the east arm of a T-maze) during 5 sessions (1 session per day; 10 trials per session). This training was followed by 2 sessions to learn strategy-2 (S2; reinforcer was in the opposite arm) that implied the extinction of S1. Five min before each session, animals received bilateral intradorsolateral-striatum injections of Noladin-ether (3.1 nM; endogen agonist of GPR55 and CB_1), CID16020036 (5.6 nM; GPR55-antagonist), AM251 (5.6 nM; CB_1 -antagonist) or a combination of Noladin-ether with each antagonist. Noladin-ether impaired evocation on the second day of S1, inducing no other changes. However, while simultaneously blocking CB_1 (with AM251), Noladin-ether improved the acquisition and evocation of S1. In contrast, while simultaneously blocking GPR55 (with CID16020036), Noladin-ether weakened S1 acquisition and evocation. CID16020036 by itself hindered acquisition of both S1 and S2. AM251 by itself induced no significant changes in the task performance. Latency to reach arms from starting point was similar among groups, thus no motor coordination impairments interfered with this task. These results strongly suggest a role of GPR55 in procedural memory and constitute the first evidence indicating this receptor regulates cognitive processes.

Disclosures: B.A. Marichal-Cancino: None. **A. Sánchez-Fuentes:** None. **M. Méndez-Díaz:** None. **A.E. Ruiz-Contreras:** None. **Ó. Prospéro-García:** None.

Poster

823. Learning and Memory: Neurotransmitter-Receptor Systems

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 823.25/CC22

Topic: F.02. Animal Cognition and Behavior

Support: MJFF

Title: Increased learning rate in a visual discrimination and reversal learning task by chronic GPR6-antagonist treatment

Authors: *H. S. LINDGREN, P. HJØRRINGGAARD LARSEN, I. VESTERGAARD KLEWE;
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Abstract: The constitutively active G-protein coupled receptor 6 (GPR6) is coupled to a stimulatory G-protein and increases the levels of cyclic AMP when activated. The receptor is predominantly expressed on striatopallidal medium sized spiny neurons but knowledge about its precise function is sparse. The importance of the striatum in various forms of rule learning and behavioural flexibility is however well documented and interestingly, GPR6 has been identified as a regulator of instrumental conditioning in mice, and genetically linked to reinforcement learning in humans. In this study, we investigated the effect of chronic GPR6-antagonist treatment on the acquisition of a visual discrimination task and reversal learning in an operant touchscreen system. Rats treated with the GPR6-antagonist learned the visual discrimination task more readily than the vehicle-treated controls with higher response accuracy during the three last days of treatment. In addition, the number of responses was overall higher in these rats compared to controls, which was speculated to reflect the increase in motor activity seen with this drug. During the reversal phase, both groups of rats reversed their behaviour and started responding to the previously non-rewarded image. However, the rats treated with the GPR6-antagonist were faster in learning the new contingencies and displayed higher response accuracy than the vehicle treated controls already after a few days of testing and remained better throughout the testing period. Initially, the number of responses was higher in the GPR6-treated rats, but this difference got smaller and diminished at the end of the testing period. The specific localisation of GPR6 to striatopallidal neurons were confirmed using *in situ* hybridisation. This study has shown that the GPR6-antagonism increases the learning rate of both a visual discrimination and reversal learning task in intact rats. Considering the nearly specific striatal expression of GPR6, drugs targeting this receptor may be beneficial in many neurological and psychiatric disorders, in which cognitive dysfunction of striatal origin is evident.

Disclosures: H.S. Lindgren: A. Employment/Salary (full or part-time):; H. Lundbeck A/S. **P. Hjørringgaard Larsen:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S. **I. Vestergaard Klewe:** A. Employment/Salary (full or part-time):; H. Lundbeck A/S.

Poster

824. Fear Memory: Neural Circuits

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 824.01/CC23

Topic: F.02. Animal Cognition and Behavior

Support: Travel Grant by Pharmacology Graduate Program of the Federal University of Santa Catarina

Title: Prelimbic cortex hyperactivation during fear memory consolidation or reconsolidation induces maladaptive behaviors outcomes in rats

Authors: *A. C. VANVOSSEN, C. A. J. STERN, M. A. M. PORTES, L. J. BERTOGLIO; Univ. Federal De Santa Catarina, Florianópolis, Brazil

Abstract: The activity of prelimbic (PL) cortex, a medial prefrontal cortex subregion, has been implicated in aversive memory consolidation and reconsolidation in rodents. The homolog human brain region of the rodent PL cortex is reported to be hyperactive in post-traumatic stress disorder (PTSD). Based on that, this study sought to investigate whether potentiating the PL cortex activity, through pharmacological glutamatergic NMDA receptor stimulation, during consolidation or reconsolidation of a contextual fear memory would induce fear generalization, a feature of PTSD involving an inability to restrict freezing to the appropriate context. In Experiment 1, male Wistar rats were fear conditioned to the context A and immediately after that received a bilateral infusion of vehicle or NMDA (30-300 pmol in 0.2 µl per hemisphere) into PL cortex. On the following days, they were re-exposed to the paired context A (Test A) and exposed to a neutral and unpaired context B (Test B). In any case, freezing behavior was measured as an index of fear memory. During Test A, all groups presented a comparable amount of freezing time, but animals infused intra-PL with 100 pmol of NMDA expressed significantly more freezing than controls during Test B (42 ± 6 vs. 15 ± 5%), indicating fear generalization. In Experiment 2, to corroborate that fear memory generalization was due to a consolidation potentiation, rats were subjected to a weaker fear conditioning and immediately after that received a bilateral infusion of vehicle or NMDA 100 pmol into PL cortex. During Test A, PL-stimulated group expressed significantly more freezing than controls (57 ± 10 vs. 30 ± 6%), indicating a potentiation of the memory consolidation, without any changes in Test B (8 ± 4 vs. 6 ± 2%). In Experiment 3, rats were submitted to a fear extinction session one day after fear conditioning. PL-stimulated group was less prone to fear extinction (69 ± 3 vs. 34 ± 9%), another PTSD-related feature. In Experiment 4, PL-stimulated group showed a more persistent contextual fear memory in Test A performed 28 d later (64 ± 5 vs. 43 ± 8%). In Experiment 5, rats were fear conditioned to the context A and had the memory reactivated by a brief re-exposure to the paired context on the next day. Immediately after that, they received a bilateral infusion of vehicle or NMDA into PL cortex. PL-stimulated group during memory

reconsolidation expressed significantly more freezing than controls during Test B (47 ± 7 vs. 17 ± 5%). Altogether, present results suggest that hyperactivity of the PL cortex is able to potentiate the consolidation and reconsolidation of recent and remote fear memories, with generation of maladaptive behavioral outcomes associated with PTSD.

Disclosures: A.C. Vanvossen: None. **C.A.J. Stern:** None. **M.A.M. Portes:** None. **L.J. Bertoglio:** None.

Poster

824. Fear Memory: Neural Circuits

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 824.02/CC24

Topic: F.02. Animal Cognition and Behavior

Support: NHMRC 1077806

Title: Effects of optogenetic stimulation of the rat lateral and ventrolateral periaqueductal gray on fear behaviour and fear learning

Authors: *N. ASSAREH, G. P. MCNALLY;
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Abstract: The midbrain periaqueductal gray is important for the expression of species-specific defense responses to threat and danger as well as for learning about such threat and danger via Pavlovian conditioning. We used adenonassociated viral vectors to express ChR2 or eNpHr3.0 in rat lateral or ventrolateral periaqueductal gray (PAG) neurons to examine the effects of optogenetic excitation and inhibition of PAG on expression of defensive behaviour and Pavlovian fear conditioning. When studying expression of defensive behaviour, lateral PAG (lPAG) ChR2 excitation caused pronounced and robust activity bursts, similar to those observed following foot shock. These bursts had very short onset latencies (< 25ms), were stimulation bound, and were dependent on the frequency (1 - 20 Hz) as well as intensity of stimulation. There was evidence for adaptation to these effects so that with repeated stimulation, the activity burst was replaced by the species-typical defense response of freezing. eNpHr3.0 inhibition of lPAG had few observable effects on behaviour. ChR2 excitation of ventrolateral PAG (vlPAG) caused expression of the species-typical defense response of freezing. Unlike lPAG, these behavioural effects were not time locked to stimulation, so that freezing emerged slowly (2 - 3 s) following stimulation onset and persisted seconds to minutes following stimulation offset, and were not obviously linked to stimulation frequency or intensity. eNpHr3.0 vlPAG inhibition had

few observable effects on behaviour. In contrast, during fear conditioning, eNpHr3.0 lPAG inhibition limited to the time of footshock delivery impaired the acquisition of fear learning whereas eNpHr3.0 vlPAG inhibition limited to the time of footshock delivery augmented the acquisition of fear. Taken together, these findings suggest that lPAG is critical to the adaptive responding to and learning about unexpected aversive events whereas vlPAG is critical to the adaptive responding to and learning about expected aversive events.

Disclosures: N. Assareh: None. **G.P. McNally:** None.

Poster

824. Fear Memory: Neural Circuits

Location: Hall A

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Topic: F.02. Animal Cognition and Behavior

Support: R01 MH099073 (J.J.K.)

NS076416 (S.J.Y.M)

KIST Intramural Grant, 2E25210 (J.C.)

Title: Neural correlates of fear in rats foraging for food and encountering a 'predatory' threat

Authors: *E. KIM[1], M.-S. KONG[1], S. PARK[3,4], M. PARK[3,4], S. J. Y. MIZUMORI[1,2], J. CHO[3,4], J. J. KIM[1,2];
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Abstract: Fear serves protective functions in animals and humans by influencing daily behaviors to reduce exposures to threats in their ecological niches. By using an ecologically-relevant "approach food-avoid predator" conflict paradigm (Choi and Kim 2010), we recently reported that a looming predatory robot induced remapping of hippocampal place fields as the animals advanced toward the vicinity of the threat and were unsuccessful in procuring food, but not when they were around the safety of the nest (Kim et al., 2015). These behavioral and neurophysiological effects were prevented by lesioning the amygdala. How amygdalar neurons respond to the immenient threat to regulate foraging decisions, however, remains unknown. Given that the amygdala is reciprocally connected with the medial prefrontal cortex (mPFC), a structure also implicated in fear regulation, we employed simultaneous single unit recordings to

investigate how cells in the basolateral amygdala (BLA) and mPFC may signal fear in foraging rats. To do so, hunger-motivated rats (85% normal body weight), implanted with tetrode arrays in the BLA and mPFC ipsilaterally, underwent successive stages of nest habituation, foraging baseline, and robot testing. Tetrodes were gradually advanced towards their target structures as the rats exited their nest in search of food pellets placed in a large open field. The robot testing consisted of 'pre-robot,' 'robot,' and 'post-robot' recording sessions. We found that both the BLA and mPFC neurons exhibited increased and/or decreased firing when the rats entered the foraging area and encountered a looming robot from distant. Specifically, the mPFC neurons showed more persistent firing than the BLA neurons. The differential time course of responses by BLA and mPFC neurons suggest that these structures make different contributions to foraging decision in the presence of a predatory threat.

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Poster

824. Fear Memory: Neural Circuits

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Topic: F.02. Animal Cognition and Behavior

Support: R01MH062122 (MF)

UCLA Brain Injury Research Center

Joseph Drown Foundation

1PO1NS058489 (DH)

1R01NS27544 (DH)

Centre for Neuroskills (DH)

Title: Stimulus-specific enhanced contextual fear learning following lateral fluid percussion experimental traumatic brain injury

Authors: *A. N. HOFFMAN[1,2], J. LAM[1], Y. CAI[2], C. C. GIZA[2], D. A. HOVDA[2], M. S. FANSELOW[1];
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Abstract: Traumatic brain injury (TBI) is a silent epidemic and is labeled the signature injury of troops in recent combat operations, a population that are often exposed to stressful stimuli and emotional trauma. While TBI is typically known to impair learning and memory for neutral events, traumatic fear memories are enhanced after TBI, consistent with increased prevalence of comorbid TBI and post-traumatic stress disorder (PTSD). Changes in sensitivity to sensory stimuli are common after TBI, and might influence the encoding of traumatic events. Our lab has shown enhanced contextual fear after lateral fluid percussion injury (LFPI) when fear conditioned after injury with white noise cues paired with footshocks (Reger et al., *Biol. Psychiatry*, 2012). In the current study we show that compared to sham, LFPI did not impact acquisition, context, or cued fear when fear conditioned with low frequency (2800Hz), pure tones. Given that white noise encompasses a greater frequency range, we hypothesize that LFPI enhances contextual fear to white noise-signaled conditioning due to injury-induced altered sensory processing. In a second experiment, LFPI or sham rats were pre-exposed to white noise trials, then were fear conditioned and tested for contextual and cued fear on subsequent days. Interestingly, LFPI rats showed elevated freezing to the white noise (16.8% vs. 4.2%, $p<0.001$) and context (32.6% vs. 7.1%, $p<0.001$) during the pre-exposure session, and during baseline the next day (6.9% vs. 1.2%, $p=0.035$), suggesting that LFPI rats conditioned to white noise alone. Furthermore, LFPI rats displayed enhanced contextual fear in the days after conditioning (day 1 freezing: 83.1% vs. 56.6%, $p=0.001$). These data provide implications for altered sensory processing after TBI, where otherwise neutral stimuli may adopt aversive properties and impact encoding of traumatic memories.

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Poster

824. Fear Memory: Neural Circuits

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Topic: F.02. Animal Cognition and Behavior

Support: RSCF grant 14-15-00685

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Title: Differential involvement of cortical areas in associative memory formation and retrieval in three versions of cued fear conditioning task in mice

Authors: *O. I. IVASHKINA[1,2], K. TOROPOVA[1,2], M. ROSHCHINA[1,2], T. KUNITSYNA[1,2], N. VOROBYEVA[1], K. ANOKHIN[1,2,3,4];
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Abstract: Associative learning is a fundamental mechanism for experience-dependent modification of the cerebral cortex. Though synaptic mechanisms of associative conditioning in the cerebral cortex have been thoroughly studied, much less is known about its representation at the level of global neuronal populations. In the present study, we compared mouse behavior in three versions of classical fear conditioning task and imaged c-Fos activity in several associative and sensory cortices after memory acquisition and retrieval. First, we studied a classical cued fear conditioning to the auditory conditional stimulus (CS). We found that association of the tone CS with the footshock resulted in activation of the ventral part of the secondary auditory cortex, while retrieval of memory in response to the auditory CS produced preferential activation of prelimbic, infralimbic and parietal associative cortices. Next, we used a compound fear conditioning, where CS consisted of the auditory (tone, T) and visual (blinking light, L) components. Mice successfully associated the compound CS with the footshock and displayed freezing response both to the entire compound CS and to its separate T and L components. Acquisition of association between the compound CS and the footshock specifically involved the prelimbic and frontal associative cortices. Retrieval of memory by the entire compound cue resulted in specific activation of the prelimbic, parietal, primary visual, secondary visual and auditory cortex, whereas retrieval by one of the components of the compound CS did not activate the parietal cortex. Finally, we developed a new model of associative conditioning with pre-exposure facilitation by adding an auditory cue to the context pre-exposure learning session. Mice received three tone stimuli in a novel neutral context and three days later were briefly (5 sec) exposed to the same context with the auditory CS followed by the footshock. In the retrieval session, mice were presented with the tone CS in a novel context. Mice that received both the initial tone pre-exposure and the 5 sec tone CS successfully associated the tone with the footshock. Thus, our data suggest that mice are able to form complex associations in different versions of the classical fear conditioning task. We also showed that the compound associative memory engages additional sensory and associative cortical areas compared to the traditional single cue fear conditioning. Moreover, acquisition and retrieval of the associative fear memory engages distinct patterns of cortical activity in mice.

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Poster

824. Fear Memory: Neural Circuits

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 824.06/CC28

Topic: F.02. Animal Cognition and Behavior

Title: Activity-dependent structural plasticity after fear conditioning in amygdala and auditory cortex pyramidal neurons

Authors: *T. GRUENE[1], K. FLICK[1], S. RENDALL[1,2], J. GRAY[2], R. SHANSKY[1];
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Abstract: The brain is highly plastic and undergoes changes in response to many experiences. Learning especially can induce structural remodeling of dendritic spines, which is thought to relate to memory formation. Pavlovian auditory fear conditioning has been widely used to study neural processes underlying learning and memory, and involves recruitment of the medial prefrontal cortex, hippocampus, amygdala and auditory association areas. Past research has found dendritic spine changes after fear conditioning in several of these structures. But, due to heterogeneity of cells within brain structures and limitations of traditional neuroanatomical techniques, it is unclear if all cells included in analyses were actually involved in fear learning, even if known circuits are isolated. In this study, we employed a novel approach to analyze structural plasticity explicitly in neurons activated by fear conditioning. We used male and female Arc-dVenus transgenic mice, which express the Venus fluorophore driven by the activity-related Arc promoter, to identify neurons that were active during fear conditioning. All mice underwent auditory fear conditioning in custom built home cages to reduce noise in Arc expression and structural plasticity induced by handling. We then targeted fluorescent microinjections to Arc+ and neighboring Arc- neurons in the basolateral area of the amygdala (BLA) and auditory association cortex (TeA). Dendritic segments were imaged in 3D using a confocal microscope and automated spine analysis was performed. In the BLA, Arc+ neurons had reduced thin and mushroom spine densities compared to Arc- neurons. This effect was present in both males and females. In the TeA, however, differences between Arc+ and Arc- neurons were not uniform across all animals. To look for additional structural differences, spine head diameters were analyzed. Overall, this study adds to our understanding of how learning affects structural plasticity, and represents a methodological advance in the ways we can directly relate structural changes to learning-related neural activity. While we did not observe sex-differences in dendritic spine changes in the BLA and TeA, future studies will need to explore if sex-differences exist in other brain regions involved in fear conditioning.

Disclosures: **T. Gruene:** None. **K. Flick:** None. **S. Rendall:** None. **J. Gray:** None. **R. Shansky:** None.

Poster

824. Fear Memory: Neural Circuits

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 824.07/CC29

Topic: F.02. Animal Cognition and Behavior

Support: R01 MH099073 (J.J.K.)

KIST Intramural Grant 2E25210 (J.C.)

Title: Amygdala is essential for hippocampal place cells to encode a distance gradient of fear in foraging rats

Authors: ***M.-S. KONG**[1], E. KIM[1], M. PARK[2,3], S. PARK[2,3], J. CHO[2,3], J. J. KIM[1,4];
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Abstract: Fear is an adaptive mechanism evolved to guide behaviors that help maximize survival while minimizing exposure to risk. Our laboratory has recently developed a relatively simple semi-naturalistic preparation to investigate the rat's foraging behavior when confronted with an artificial predator (assembled from LEGO Mindstorms robotic kit) programmed to surge toward the animals seeking food (Choi and Kim, 2010). Our initial work revealed that while the rats were unable to acquire food pellets placed distal from the safety of the nest (i.e., near the predatory robot), they were able to secure pellets placed nearby the nest. This suggests that fear significantly reduced the distance the rats will travel to intercept food and that the animals formed a spatial gradient of fear or defensive distance from the source of threat. Very recently, we reported that the hippocampal place cells exhibited differential activity patterns during the foraging task (Kim et al, 2015). The surging robot induced transient remapping of place fields near the source of threat (i.e., distal to the nest), whereas those fields adjacent to or inside the nest were relatively stable. The present study investigated whether the transient remapping of distal place fields is in fact due to fear by recording place cells in rats where the robot was stationary and in amygdala-lesioned rats. A pixel-by-pixel correlation analysis indicated that with a stationary robot, hippocampal place cells were comparably stable in all foraging area. In amygdala-lesioned animals, the looming robot affected neither the foraging behavior nor the

stability of place fields in the distal area. These results indicate that the amygdalar signaling of fear evoked by the looming motion, and not the salience/novelty, of the robot influences the stability of hippocampal place cells as a function of threat distance in rats foraging for food.

Disclosures: **M. Kong:** None. **E. Kim:** None. **M. Park:** None. **S. Park:** None. **J. Cho:** None. **J.J. Kim:** None.

Poster

824. Fear Memory: Neural Circuits

Location: Hall A

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Program#/Poster#: 824.08/CC30

Topic: F.02. Animal Cognition and Behavior

Support: ASU College of Liberal Arts and Sciences (Conrad)

Title: Fear conditioning using a two-tone discrimination paradigm: Potential use for chronic stress investigations

Authors: ***J. M. JUDD**, K. J. NISHIMURA, C. R. ARNETT, F. SANABRIA, C. D. CONRAD; Psychology, Arizona State Univ., Tempe, AZ

Abstract: In the laboratory, variations of fear conditioning are frequently used as a model of post-traumatic stress disorder, as it pertains to fear memory formation, extinction, and reconsolidation. In fear conditioning, pairing a neutral stimulus, such as tone (conditioned stimulus, CS), with an unconditioned stimulus (US) can eventually lead to the CS eliciting a freezing response. Freezing to the CS in the absence of the US is a conditioned response (CR), due to an association between the CS and the US. The amount of freezing to the tone alone can be used as an indicator of the strength of the fear memory. Typically in the stress and fear conditioning field, researchers use a between-subject design, in which one set of animals is used to investigate the CS/US paired outcome and another set is a control in which the CS is explicitly unpaired from the US. The unpaired group allows the researcher to determine whether the CR is associative or non-associative. Other conditioning paradigms use a within-subject design, which have the benefits of reducing subject number, lowering the inter-subject variability, and providing higher power. We determined if a within-subject design could be used in fear conditioning by employing a discriminative fear conditioning paradigm, in which animals were exposed to both a predictive tone (CS+) and a non-predictive tone (CS-). This method is a powerful way to target a specific fear memory and explore the effect a treatment would have on fear memory persistence. Male Sprague-Dawley rats were used. Fear conditioning consisted of a

training day (CS+ and CS-), reactivation 24-hrs later (one CS+ only), post-reactivation short-term memory (PR-STM 4 hrs later with CS+ and CS-) and post-reactivation long-term memory (PR-LTM, with CS+ and CS-) 24-hrs after reactivation. In the first study, we used variations of tone to optimize discrimination as follows: three tone sets (3 CS+ and 3CS-), 7kHz tone range (3kHz vs 10kHz), tone persistence (continuous vs pulses 100 ms on and 100 ms off). In the second study, modifications to the tones were as follows: five tone sets (5 CS+ and 5CS-), 12kHz tone range (3kHz vs. 15kHz), tone persistence (continuous vs 100 ms on and 200 ms off). Rats had difficulty maintaining discrimination across days with three sets of CS+/CS-. However, rats discriminated with five CS+/CS-, but extinguished quickly by PR-LTM. As part of a larger study, we plan to implement a five CS+/CS- training paradigm with three CS+/CS- during PR-STM and PR-LTM to investigate mechanisms of reconsolidation after chronic stress.

Disclosures: **J.M. Judd:** None. **K.J. Nishimura:** None. **C.R. Arnett:** None. **F. Sanabria:** None. **C.D. Conrad:** None.

Poster

824. Fear Memory: Neural Circuits

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Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant RO1MH062122

Title: The indirect pathway from entorhinal cortex to CA3 should be used during recall of hippocampal conjunctive representations

Authors: *F. B. KRASNE[1,2], M. S. FANSELOW[1,2,3], J. D. CUSHMAN[1];
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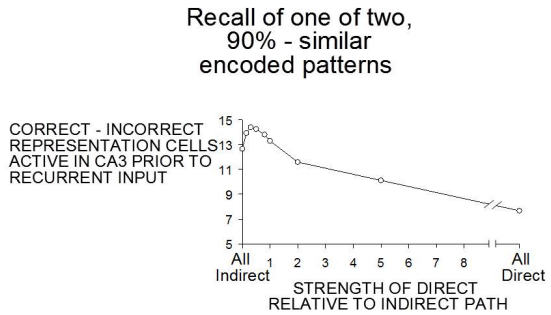
Abstract: It is widely believed that the hippocampus creates long-persisting representations of complex stimuli to which associations can be made. For example, during context fear conditioning the hippocampus creates a representation of the conjunction of a context's attributes to which fear becomes conditioned in the amygdala. There is consensus that representations are expressed within CA3 and that they are encoded as synaptic potentiation in CA3's system of recurrent collaterals. CA3 receives "direct" input from EC and "indirect" input from EC via dentate (DG). There is wide agreement that which CA3 cells will comprise a representation is determined by which DG cells are most excited by EC input during the representation's creation;

however, it has been argued that in order to prevent this selection process from being distorted by interference from the recurrent collaterals, DG-CA3 synapses must be overridingly effective. But, it is then argued that such strong DG-CA3 synapses preclude use of the indirect pathway for activation of the correct representation of a familiar context on subsequent recall occasions because input from the recurrent collaterals would be overshadowed by DG input (Treves and Rolls, 1992). However, we see no reason why DG-CA3 transmission should not simply be up-regulated during representation creation (see Krasne et al, 2015). We therefore investigated the relative merits of using only the direct, only the indirect, or various balances of the two pathways to CA3 during recall, using a computational model of hippocampal function (BACON, Krasne et al, 2015). Consistent with theoretical expectations, the indirect pathway alone provides better recall than the direct alone, but both together are best. Moreover, to be helpful, the direct pathway must be quite weak; the distal location of direct path inputs in the biological hippocampus is consistent with this. We therefore believe that computational considerations should not be used to discount a major role for the indirect pathway in recall.



Disclosures: **F.B. Krasne:** None. **M.S. Fanselow:** None. **J.D. Cushman:** None.

Poster

824. Fear Memory: Neural Circuits

Location: Hall A

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Title: Modulating innate fear based on visual stimulus by a novel subcortical pathway in mice

Authors: ***N. LIU**, P. WEI, X. LIU, Y. TANG, Y. LIU, Z. ZHOU, L. WANG;
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Abstract: The innate ability of animals to respond to life-threatening stimuli is essential for survival. These stimuli activate modular brain circuits consisting of phylogenetically ancient subcortical structures, however, details regarding the circuitry mechanisms responsible for processing innate threat stimuli remain to be elucidated. Here,we investigate the circuitry underlying innate defensive behaviors elicited by predator-like visual stimuli in mice. Our results demonstrate that neurons in the superior colliculus (SC) are essential for a variety of acute and persistent defensive responses to overhead looming stimuli, and phasic optogenetic activation of these neurons or their terminals projecting to lateral posterior thalamic nucleus (LP), a non-canonical polymodal sensory relay, is sufficient to elicit similar defensive behaviors, such as unlearned long lasting freezing, followed by sustained avoidance and anxiety-like behavior. Using trans-synaptic tracing in conjunction with *in vivo* electrophysiology experiments, we figured out a di-synaptic circuit from SC through LP to the lateral amygdala (LA), and inhibition of the amygdala blocked the full range of defensive responses. Taken together, Our results revealed a novel SC-LP-LA subcortical pathway that conveys visual threat information, leading to innate, fear-related defensive behaviors.

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Poster

824. Fear Memory: Neural Circuits

Location: Hall A

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Topic: F.02. Animal Cognition and Behavior

Support: R01 MH099073 (J.J.K)

Title: Dissociation of the medial and lateral habenula in the expression of unconditioned defensive behavior

Authors: *B. A. PELLMAN[1], E. KIM[1], Y. RAO[1], J. J. KIM[1,2];
[1]Dept. of Psychology, [2]Program in Neurosci., Univ. of Washington, Seattle, WA

Abstract: Both the medial and lateral habenula (MHb and LHb, respectively) have been implicated in processing information about aversive events in the environment (Viswanath et al., 2014). Neurons in the LHb increase activity when an animal is presented with an unexpected aversive stimulus, such as the absence of an expected reward or the presence of punishment (Matsumoto & Hikosaka, 2009). Correspondingly, lesions/inactivations of the LHb impair avoidance learning and memory while its stimulation enhances avoidance learning (Pobbe & Zangrossi, 2008; Stamatakis & Stuber, 2012). While less is known about the functions of the MHb, some evidence suggests that it may play an opposing role to the LHb (Bjartmer et al., 2010; Viswanath et al., 2014). The present study compared the roles of the LHb and MHb in rats utilizing an ethologically-relevant 'approach food-avoid predator' paradigm and classical fear conditioning to assess both unconditioned defensive behaviors and conditioned fear responses. Rats received either electrolytic lesions to the LHb or MHb or sham lesions. They were then trained over 4 days in an elongated open field to retrieve grain pellets at increasing distances from a safe 'nest' area to which they had previously been habituated. Subsequently, a LEGO® Mindstorms® robot shaped like an alligator and programmed to surge forward and snap its 'jaws' when rats approached the pellets was placed opposite of the 'nest' area, and the rats attempted to retrieve the pellets while avoiding the predator-like robot (cf., Choi & Kim, 2010). After testing with the robot on days 1, 2 and 9, rats underwent auditory fear conditioning and freezing to the tone and context were assessed independently 24 h later. Lesions of the MHb impaired the ability of rats to obtain the pellet across all distances relative to sham controls, whereas LHb lesions reduced the time rats took to obtain the pellet at farther distances relative to sham controls. Thus, MHb-lesioned animals showed sustained heightened fear across all three days of exposure to the robot while LHb-lesioned animals exhibited reduced fear and faster habituation to the false threat of the robot compared to sham control animals. In contrast, there were no differences between groups during the acquisition or expression of fear conditioning to the tone or context. These results seem to suggest that the MHb and LHb play opposing roles in unconditioned avoidance responses but are not critical for the acquisition or expression of conditioned freezing.

Disclosures: B.A. Pellman: None. **E. Kim:** None. **Y. Rao:** None. **J.J. Kim:** None.

Poster

824. Fear Memory: Neural Circuits

Location: Hall A

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Topic: F.02. Animal Cognition and Behavior

Support: FAPESP: 2010/50669-6

Title: Behavioral, neuroanatomical, neuroendocrine and neurochemical features of the expression phase of fear conditioning to a light-CS

Authors: *A. R. OLIVEIRA[1,2], A. E. REIMER[3,2], L. ALBRECHET-SOUZA[2,4], F. M. C. V. REIS[3,2], M. C. CARVALHO[3,2], M. L. BRANDÃO[3,2];
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Abstract: The Pavlovian fear conditioning is one of the most common paradigms used to study the biological basis of emotion, as well as of learning and memory. Considering the complexity of defensive response expression, several interactions between diverse stress mediators acting in distinct brain structures may be required for optimal performance in front of aversive conditioned stimuli (CS). In this direction, the mesolimbic dopamine (DA) pathway is being demonstrated to have an important role in states of fear and anxiety. On the other hand, the activation of the hypothalamic-pituitary-adrenocortical (HPA) axis, reflected by an increase in plasma corticosterone in rodents, has been considered a key part of the stress reaction. In previous studies, we showed that corticosterone upregulates the dopaminergic neurotransmission in the ventral tegmental area (VTA)-basolateral amygdala (BLA) pathway, which facilitates the expression of conditioned fear responses. In the present study, we aimed to expand the characterization of the expression phase of fear conditioning using a light-CS. For this, separate groups of animals were submitted to one training session in which they were exposed to 10 non-paired presentations of light and footshocks (control group) or 10 pairings of light and footshocks (conditioned group). Twenty-four hours after training, animals were subjected to 10 presentations of light during a test session that lasted 20 minutes, in a different cage from that used during the training session. An additional group of animals that did not pass by the training or testing sessions was also used (no stress group). The parameters monitored included the conditioned freezing response, the distribution of Fos protein in the VTA and amygdala, the plasma concentrations of corticosterone, and the tissue content of DA and metabolites in the amygdala. Rats previously subjected to paired presentations of light and footshocks exhibited a robust increase in the time spent freezing compared with controls. Light-CS also promoted a significant increase in the number of Fos-positive cells in the VTA, but not in the amygdala. A general increased plasma corticosterone concentration was associated with exposure to the conditioned fear protocol. No differences in DA, DOPAC or HVA concentrations in the amygdala were observed after exposure to light-CS in conditioned group compared to control.

Although more investigation is needed to clarify this field, the data obtained in the present work bring additional evidence to the notion that a complex interaction of stress mediators acting in different brain areas play a role in the expression of conditioned fear to a light-CS.

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Poster

824. Fear Memory: Neural Circuits

Location: Hall A

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Topic: F.02. Animal Cognition and Behavior

Support: NIMH Grant R01 MH62122

Title: Chemogenetic inhibition of the ventromedial prefrontal cortex increases fear generalization and impairs fear extinction

Authors: *Z. T. PENNINGTON, J. Z. AVERSHAL, A. S. ANDERSON, M. S. FANSELOW; Dept. of Psychology, UCLA, Los Angeles, CA

Abstract: Post-traumatic stress disorder is associated with both structural and functional changes in the ventromedial prefrontal cortex (vmPFC). Evidence indicates that the vmPFC is important in mediating the extinction of responses to feared stimuli, suggesting that these anomalies may be responsible for the pervasiveness of symptoms. Nevertheless, both human and rodent studies suggest that the vmPFC is also integral to reducing fear to stimuli similar to those that have been paired with an aversive event (i.e. fear generalization), a behavioral phenomenon that is also clinically relevant. The present work was undertaken as a foray into parsing the contribution of the vmPFC to fear extinction and fear generalization. Designer receptors exclusively activated by designer drugs (DREADDs) were used to inhibit the infralimbic subregion (IL) of the rat vmPFC while animals were tested for the acquisition, generalization, and extinction of a fear memory. Subsequently, anxiety in response to IL inhibition was assessed in an open field. Although IL inhibition did not alter the acquisition of a fear memory, it did result in greater freezing to a novel context following fear conditioning, indicative of heightened fear generalization. Additionally, IL inhibition during extinction training resulted in subsequently poorer recall of the extinction memory when animals were tested drug free. Notably, inhibition of the IL neither altered the total distance traveled nor the time spent in the center of an open field, suggesting that IL inhibition does not reduce locomotor activity or induce anxiety. Using transient chemogenetic

inhibition, these findings replicate the findings that the IL is important for both fear generalization and fear extinction. Future studies aim to use both pathway- and temporally-specific manipulations to understand how dysfunction of the vmPFC alters these processes.

Disclosures: Z.T. Pennington: None. **J.Z. Avershal:** None. **A.S. Anderson:** None. **M.S. Fanselow:** None.

Poster

825. Decision Making: Neuropharmacology

Location: Hall A

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Topic: F.03. Motivation and Emotion

Support: NWO-Veni to HdO, grant nr. 451-11-004

HFSP to RC and ND, grant nr. RGP0036/2009-C

James McDonnell scholar award to RC

Title: Serotonin, affective biases and prefrontal control

Authors: *H. E. DEN OUDEN[1], D. E. M. GEURTS[2], K. SCHMIDT[3], N. D. DAW[4], R. COOLS[1];
[1]Donders Inst. for Brain, Cognition and Behaviour, [2]Dept. of Psychiatry, Radboud Univ., Nijmegen, Netherlands; [3]Dept. of Psychiatry, Oxford Univ., Oxford, United Kingdom; [4]Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Serotonin (5HT) is implicated in both aversive processing[1,2] and behavioral inhibition[3], with evidence showing that a reduction in 5HT disinhibits behavior in the face of expected punishments[4,5]. Indeed a popular recent idea is that 5HT has a specific role in tying aversive Pavlovian influences to instrumental inhibition[6-9]. To test this idea, we pitted the Pavlovian and instrumental control systems against each other, by varying instrumental demands while keeping the Pavlovian value of the cue constant. We manipulated 5HT levels using tryptophan depletion in 50 participants who performed this task in the fMRI scanner (randomised double blind within-subject design). On each trial, a cue informed subjects whether they were playing for a reward (versus neutral) or punishment, consisting of primary reinforcers in the form of lemonade vs. a bitter solution. They chose to respond (Go) or not (NoGo), in order to get the desired outcome. As expected, participants showed a strong Pavlovian bias: they were both faster and more likely to make a Go response when playing to get a reward than to avoid punishment.

There were, surprisingly, no behavioural effects of lowering 5HT levels. However, we observed a striking difference in their neural responses. In the control condition the dorsolateral prefrontal cortex showed an increased response when participants made a Pavlovian 'incongruent' (Go2avoid or NoGo2win) response, compared to making a congruent response. This is line with previous findings that the degree of frontal response to incongruent cues predicts our ability to suppress the Pavlovian bias [10]. However, when 5HT levels were lowered, this prefrontal response was abolished. This effect was independent of cue valence. Thus, while people were equally capable of making the incongruent response, we speculate that less prefrontal control was required to override the Pavlovian bias. This finding supports our idea that 5HT is particularly important in implementing automatic affective biases responding. 1 Graeff FG, Guimaraes FS, De Andrade TG & Deakin JF (1996) *Pharmacology, biochemistry, and behavior* 2 Deakin JF & Graeff FG (1991) *J Psychopharmacology* 3 Soubrie P (1986) *Behavioral and Brain Sciences* 4 Crockett MJ, Clark L, Apergis-Schoute AM, Morein-Zamir S & Robbins TW (2012) *Neuropsychopharmacology* 5 Crockett MJ, Clark L & Robbins TW (2009) *J Neuroscience* 6 Boureau YL & Dayan P (2011) *Neuropsychopharmacology* 7 Cools R, Nakamura K & Daw ND (2011) *Neuropsychopharmacology* 8 Dayan, P. & Huys, Q. J. (2008) *Plos Computational Biology* 9 Daw ND, Kakade S & Dayan P (2002) *Neural Networks* 10 Cavanagh JF, Eisenberg I, Guitart-Masip M, Huys, Q & Frank MJ (2013) *J Neuroscience*

Disclosures: H.E. Den Ouden: None. **D.E.M. Geurts:** None. **K. Schmidt:** None. **N.D. Daw:** None. **R. Cools:** None.

Poster

825. Decision Making: Neuropharmacology

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Program#/Poster#: 825.02/CC37

Topic: F.03. Motivation and Emotion

Support: The Finnish Foundation for Alcohol Studies Grant

Orion Pharma Grant

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Title: Opioidergic modulation of cost-benefit decision making of AA rats in rat Casino-model

Authors: *V. OINIO[1,2], P. BÄCKSTRÖM[2], J. UHARI-VÄÄNÄNEN[1], A. RAASMAJA[1], K. KIIANMAA[2], P. PIEPPONEN[1];
[1]Univ. of Helsinki, Helsinki, Finland; [2]Natl. institute for health and welfare, Helsinki, Finland

Abstract: Co-morbidity with gambling disorder (DSM-5) and substance abuse disorders, especially alcohol use is well documented and might share same neuronal pathways including opioidergic systems. Aim of the study was to study cost-benefit decision making of alcohol-preferring AA (Alko Alcohol) rats and whether it can be modulated by opioidergic agents. We developed the Casino-model of rodent gambling, which resembles the situation when gamblers go to casino over and over again despite knowing the fact that casino "always wins". The model is based on operant probabilistic discounting i.e. devaluing a reinforcer by decreasing the probability of obtaining it and eventually stabilizing the probability to level where single high rewards can be received by expense of many smaller, but in long run, more profitable rewards. Male alcohol preferring AA rats were trained to self-administer sucrose pellets (45 mg) in a two-lever choice task. One lever was designated as SS-lever ("Small-Sure") which delivered one sucrose pellet always at probability of 100% and other was designated as LL-lever ("Large-Lucky") which delivered three sucrose pellets at decreasing probabilities (100%, 50%, 33% and 25%). Duration of one session was 24 trials (called "credits") or 30 minutes. First the rats were taught to make rational decisions based on one versus three sugar pellet rewards (probability for receiving both 100 %). Rats that could not perform rational decision making behavior were disqualified. After rational behavior was reached the probability for obtaining pellets from LL-lever was decreased over time to a probability level of 25 % (Casino-level), thus at the Casino-level by choosing the LL-lever the rats received calculatory only 0.75 pellets by each credit. The effects of morphine (n=12) and naltrexone (n=11) were examined at the Casino-level. Both drugs were administered s.c. at two different doses (0.3 mg/kg and 1.0 mg/kg). Morphine decreased AA rats LL-lever choices significantly compared to vehicle in dose dependent manner. Morphine had no effect on played "credits" or time spend to consume these. Naltrexone had no significant effects to lever choices but had trend to decrease amount of played "credits" and increased significantly the time that rats spend to consume these. Results indicate that reward guided cost-benefit decision making can be modulated by opioidergic agents, especially with alcohol preferring AA rat strain.

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Poster

825. Decision Making: Neuropharmacology

Location: Hall A

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Program#/Poster#: 825.03/CC38

Topic: F.03. Motivation and Emotion

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Title: Content analysis of dreams induced by an alleged oneirogenic plant: Calea zacatechichi

Authors: *A. ROSALES-LAGARDE[1], L. MAYAGOITIA[2], J. GONZÁLEZ[3], J. DÍAZ[4]; [1]Inst. de Ciencias de la Salud, Área Académica de Gerontología, CONACYT-UAEH, Tilcuautla, Mexico; [2]Inst. Nacional de Psiquiatría Ramón de la Fuente, DF, Mexico; [3]Univ. Autónoma del Estado de Morelos, Cuernavaca, Mexico; [4]Univ. Nacional Autónoma de México, DF, Mexico

Abstract: Calea zacatechichi (Asteraceae), a shrub employed in traditional mexican medicine has been used as appetizer, antipyretic, antidiarrhetic and cholagogue. Considered to be in non-controlled studies oneirogenic and cognodsyleptic, it rarely produces hallucinations. A double blind counterbalanced repeated measures experimental design to evaluate physiological, behavioral and psychological effects of zacatechichi appeared in 1986. Evidence in that paper pointed to an increase on frequency and colorfulness of dreams with the methanol extract, but most dreams measured by the number of lines written in the report were shorter than 5 lines. A content analysis with Hall and Van de Castle scales was undertaken to further explore the detailed complexity of short dreams considering RT tasks and subsequent night dreams. College and graduate students free from drugs or pathological or neurological antecedents (3 women and a man) gave their written consent. From the leaves and stem of the plant, hexane and methanol were used to obtain two extracts. Placebo (PL), hexane (H) or methanol (M) capsules (30 mg/Kg and 86 mg/Kg, respectively) were administered in a double blind random procedure an hour before subjects performed RT tasks while physiological measures were simultaneously recorded. All sessions began at noon and 7 days elapsed at least between sessions. Ad hoc questionnaires were used to collect dreams after the experimental tasks and after that night. For each dream and condition, word count was obtained and its content analyzed and categorized in characters, settings, actions, emotions, interactions, modifiers, temporal and negative scales and statistical analysis were carried out with real and incongruent categories. Interrater reliability by two blind judges was 95%. Mean for each category was calculated and results were submitted to the non-parametric Friedman tests. Only characters between PL and M and settings among PL and M; H and M conditions, reached significance. In two subjects word count as well as number of dreams were especially greater with the extracts. Real content was also near of reaching significant results and incongruent content was found in 36.3% of the M dream reports. C. zacatechichi during naps has been reported to increase stage 1 and awakenings, while REM sleep stage decreases. The Hall and Van de Castle method seems useful for the analysis of shorter dreams induced by oneirogenic extracts. Oneiric experience with the administration of C. zacatechichi

while performing RT tasks and during the subsequent night appears to be short, colorful, includes characters and settings and tends to have real content.

Disclosures: **A. Rosales-Lagarde:** None. **L. Mayagoitia:** None. **J. González:** None. **J. Díaz:** None.

Poster

825. Decision Making: Neuropharmacology

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 825.04/CC39

Topic: F.03. Motivation and Emotion

Support: ERC

Title: Role of serotonin in the motivational control of behavior: a pharmacological challenge in humans

Authors: ***N. BORDERIES**[1], R. LEBOUC[1], F. MEYNIEL[2], J.-C. CORVOL[1], F. VINCKIER[1], M. PESSIGLIONE[1];
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Abstract: Serotonin signaling in the brain is an important system for the motivation of behavior. It has been associated in particular with aversive processing, impulsivity and inhibitory control. It is also the target of the most prescribed antidepressant drugs, such as citalopram (a serotonin reuptake inhibitor). However, we still lack a mechanistic understanding that would articulate the role of serotonin in various motivational processes such as effort production, decision making and instrumental learning We conducted a randomized, cross-over, double-blind, placebo-controlled experiment in which a group of healthy subjects were administered an acute dose of citalopram while they were tested on a comprehensive battery of motivational tasks. Significant effects of citalopram included a reduced sensitivity to monetary incentives in effort production (force task) and a consistent reduced willingness to accept effort or punishment costs in order to get rewards (choice task). These two effects can be explained by a common down-regulation of positive expectations in the cost-benefit calculation that determines the intensity and orientation of behavior. These results suggest a role for serotonin in motivational control that is in line with the alleged opponency to dopamine, which has been shown to amplify reward sensitivity in similar tasks. This might also explain the affective blunting of appetitive expectations that has been observed in depressed patients treated with serotoninergic medication.

Disclosures: **N. Borderies:** None. **R. LeBouc:** None. **F. Meyniel:** None. **J. Corvol:** None. **F. Vinckier:** None. **M. Pessiglione:** None.

Poster

825. Decision Making: Neuropharmacology

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: F.03. Motivation and Emotion

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HFSP to RC, grant nr. RGP0036/2009-C

James McDonnell scholar award to RC

NWO-Veni to HdO, grant nr. 451-11-004

Title: Should I stay or should I go? Individual differences in effects of methylphenidate on the affective biasing of instrumental action

Authors: ***J. C. SWART**[1], J. L. COOK[1,2], M. I. FROBÖSE[1], S. J. FALLON[1,3], D. E. M. GEURTS[1,4], R. COOLS[1,4], H. E. M. DEN OUDEN[1];
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Abstract: Motivational valence influences behavioural activation in a seemingly Pavlovian manner, such that a reward context promotes activation and a punishment context promotes inhibition. Both human and animal research has shown that dopamine modulates these affective biases. In this study we aimed to assess whether i) dopamine-induced changes in affective biases should be understood as altered action execution (activation/inhibition) or as altered learning (credit assignment), and ii) how these effects depend on individual differences in measures predictive of baseline dopamine function. We tested 102 participants once after placebo and once after administration of the dopamine/noradrenalin transporter blocker methylphenidate (MPH). MPH-induced changes were predicted by individual differences in working memory (WM) capacity; MPH strengthened the Pavlovian biases proportional to WM capacity. These changes were explained by altered global activation/inhibition rather than credit assignment. In this poster session, I will discuss the differential influence of MPH on affective biases and instrumental

learning, and thereby emphasise the importance of taking into account individual differences when understanding the effects of methylphenidate.

Disclosures: **J.C. Swart:** None. **J.L. Cook:** None. **M.I. Froböse:** None. **S.J. Fallon:** None. **D.E.M. Geurts:** None. **R. Cools:** None. **H.E.M. den Ouden:** None.

Poster

825. Decision Making: Neuropharmacology

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 825.06/CC41

Topic: F.03. Motivation and Emotion

Title: The effects of stress on effort-based decision making: evidence from one model

Authors: *E. E. HART, A. STOLYAROVA, T. R. MINOR, A. IZQUIERDO;
UCLA, Los Angeles, CA

Abstract: In order to survive, animals and humans must conduct cost-benefit analyses wherein the cost of emitting a reward-seeking action is weighed against the value of its reward. Common costs of reward-seeking actions include time, risk, and effort. Effort-based decision-making has been modeled in rodents with effort requirements ranging from physical to attentional, with the former as most studied. Stress affects performance in several tests of cognition and decision-making ranging from altered memory formation (Sun & Alkon, 2014) in humans and impaired reversal learning in rodents (Campeau et al. 2011). Recent reports show effects of stress in an operant task assessing effort (Shafiei et al. 2012) and alterations in cognitive flexibility following exposure to a rat model of post-traumatic stress disorder (George et al. 2015). It is well established that effortful choices (and effort discounting) is mediated by dopamine signaling (Salamone & Correa 2012, Denk et al. 2005), which is also impacted by stress (Arnsten, 2000). Moreover, brain regions affected by stress (e.g. mPFC, BLA, NAc) are also implicated in effort. However, the effects and mechanisms of stress on effort-based decision making have not been extensively studied. For these reasons, we investigated effort-based decision making on a maze task with three possible courses of action, each associated with different effort requirements and reward magnitudes. Behavioral testing was conducted in a standard eight-arm radial maze. Four arms were permanently blocked, leaving a start arm and three choice arms. One arm of the maze was randomly designated as a low-effort/reward arm (LER, 1/2 cereal loop), another as a medium-effort/reward arm (MER, 1 cereal loop), and a third as a high-effort/reward arm (HER, 2 cereal loops). The arm containing low reward was unimpeded by a barrier, but to obtain a medium or high reward, rats were required to climb a 20 or 30 cm barrier, respectively. Male S-

D rats (n=12) received pretraining on this task before being administered shock (100, 1.0 mA tail shocks, 60s variable interval, 8s variable duration). Testing took place 24 hours after stress and had no effect on the pattern of HER, MER, and LER choices. In a control task where each reward magnitude choice had the same low effort requirement, rats did not show a preference for the high-reward magnitude option, suggesting augmented habitual control of choice behavior. Taken together, these data suggest that effort costs and habits may interact in controlling choice behavior. Further research will examine the effects of stress in other tests of effort in addition to brain mechanisms including adenosine, dopamine and acetylcholine signaling.

Disclosures: **E.E. Hart:** None. **A. Stolyarova:** None. **T.R. Minor:** None. **A. Izquierdo:** None.

Poster

825. Decision Making: Neuropharmacology

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 825.07/CC42

Topic: F.03. Motivation and Emotion

Support: James McDonnell Scholar Award

Title: Methylphenidate alters decision making about cognitive control

Authors: ***M. I. FROBOSE**[1], J. C. SWART[1], J. L. COOK[2], D. E. M. GEURTS[1], S. J. FALLON[3], H. E. M. DEN OUDEN[1], R. COOLS[1,4];
[1]Donders Ctr. for Cognitive Neuroimaging, Radboud Univ. Nijmegen, Nijmegen, Netherlands; [2]City Univ. London, London, United Kingdom; [3]Exptl. Psychology, Univ. of Oxford, Oxford, United Kingdom; [4]Dept. of Psychiatry, Radboud Univ. Med. Ctr., Nijmegen, Netherlands

Abstract: Methylphenidate is frequently prescribed for ADHD, but is also taken by healthy adults for cognitive enhancement (Maher, 2008). Elucidating the neurocognitive consequences of methylphenidate is a key scientific puzzle, given that estimates of the proportion of healthy students and academics using drugs like methylphenidate off-label range between 4% and 16% (Farah et al., 2004). Pharmacologically, methylphenidate has been found to be a potent blocker of the dopamine transporter (DAT(Ritz et al., 1987, Gatley et al., 1999), leading to increased dopamine and noradrenaline in prefrontal cortex (Berridge et al., 2006) and striatal areas (Volkow et al., 2001). Optimal catcholamine levels in the prefrontal cortex are necessary for efficient cognitive control (Brozoski et al., 1979; Berridge and Arnsten, 2012). However, the mechanisms underlying these effects are unclear. We build on recent insights that reconceptualize cognitive control as a cost-benefit decision (Shenhav et al., 2013; Westbrook and

Braver, 2015) and asked whether methylphenidate altered decision making about cognitive control. Specifically, we employed a demand selection task, developed by Kool et al (2010) to assess the degree to which subjects avoid a mentally effortful task, involving frequent task-switching. A double-blind, placebo-controlled, within-subject design was employed, where 100 healthy adults were administered placebo on one day and methylphenidate (20 mg, oral) on another. In keeping with our hypothesis, results revealed significant effects of methylphenidate on demand selection. Notable, we could isolate these effects only because we took into account individual differences in baseline working memory capacity, which is suggested to correspond with individual differences in baseline levels of striatal dopamine synthesis capacity (Cools et al., 2008). Demand avoidance was decreased in subjects with low working memory capacity, consistent with its cognitive enhancing effects in ADHD (Berridge and Arnsten, 2015). By contrast, methylphenidate increased demand avoidance in subjects with high working memory capacity, thus impeaching its cognitive enhancing potential in healthy, high-functioning healthy volunteers. Together these data demonstrate that methylphenidate alters cognitive control, by modulating decision making about cognitive control, in a baseline-dependent manner. This result concurs with current knowledge about (striatal) dopamine's role in cost-benefit decision making.

Disclosures: **M.I. Frobose:** None. **J.C. Swart:** None. **J.L. Cook:** None. **D.E.M. Geurts:** None. **S.J. Fallon:** None. **H.E.M. den Ouden:** None. **R. Cools:** None.

Poster

825. Decision Making: Neuropharmacology

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 825.08/CC43

Topic: F.03. Motivation and Emotion

Support: Wellcome Trust Research Career Development Fellowship (090051MA)

Medical Research Council UK

Title: Action initiation shapes mesolimbic dopamine encoding of future rewards

Authors: E. C. J. SYED[1], L. L. GRIMA[2], P. J. MAGILL[1], P. BROWN[1], *M. E. WALTON[3]; [1]MRC Brain Network Dynamics Unit, [2]Dept. of Exptl. Psychology, [3]Univ. of Oxford, Oxford, United Kingdom

Abstract: It is widely held from electrophysiological and electrochemical studies that dopamine signalling encodes predictions of future rewards and such predictions are regularly used to drive

behaviour. Moreover, manipulations of mesolimbic dopamine demonstrate that dopaminergic transmission is not only required to drive behavioural responses to incentive cues but can also facilitate action initiation. However, to date, the precise relationship between cue-elicited dopamine release, reward prediction, response choice and movement remains ambiguous. To investigate this issue, we used fast-scan cyclic voltammetry to monitor dopamine release in the nucleus accumbens core (NAcc) while animals performed variants of a task that required them either to initiate or withhold an action to gain reward. Following an initial response, a cue instructed the animals either to maintain their position (No-Go) or to disengage and press a lever (Go). Rats learned to perform this task with high accuracy across conditions, responding rapidly on Go trials and refraining from responding for > 2s on No-Go trials. Dopamine levels rapidly increased after cue presentation on correctly performed Go trials, the signals evolving rapidly as animals progressed through a sequence of discrete actions to gain reward. By contrast, no such change was observed on trials where a response was withheld until a response was made to collect the reward. Importantly, it was not the case that all actions resulted in dopamine release: dopamine levels on erroneously performed Go or No-Go trials also failed to elicit any change in dopamine even during or after a movement was made. Together, these results indicate that dopamine release in this region is contingent upon correct action initiation and not just reward prediction.

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Poster

825. Decision Making: Neuropharmacology

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 825.09/CC44

Topic: F.03. Motivation and Emotion

Support: NIH R21 DA036660

Title: Phasic dopamine release in the nucleus accumbens shell encodes the individual difference in impulsive decision making

Authors: ***X. XIE**, L. WILSON, B. GUZIK, C. LEE, L. QI, K. BLANTON, L. SOMBERS; Chem., North Carolina State Univ., Raleigh, NC

Abstract: High impulsivity is associated with vulnerability to cocaine relapse and treatment failure in cocaine addicts. Remarkably, impulsivity can be elicited by chronic cocaine administration, given that passive chronic cocaine exposure regimens enhance impulsivity in laboratory animals, using the delay discounting paradigm. However, little is known about the neural mechanisms underlying this behavior phenomenon. To this end, rats were surgically implanted a carbon fiber micro-electrode into the nucleus accumbens (NAC) shell region. Following recovery from surgery, rats received once daily delay discounting task training session in a standard operant conditioning chamber. The training session involved three types of contingencies (30 trials each) intermixed within 90 total trials. The presentation of these reward contingencies allowed animals to fully learn the predictive associations of the cue lights and the reward contingencies (i.e. one sucrose pellet immediately delivered or two sucrose pellets delivered after 2s delay period). Animals were trained on the task for at least 10 sessions to achieve stable performance, and electrochemical recordings of dopamine transients in the NAC shell were conducted during the first day and last day of training. Our results have shown that there is an individual difference in the preference of large delayed reward across the group of rats. Given that phasic dopamine release from the ventral tegmental area (VTA) into the NAC encodes reward delay and reward magnitude, we hypothesize that the choice reward contingency will be positively correlated with the magnitude of cue-evoked dopamine release in the NAC during the performance of impulsive decision making task. This line of study will help understand the neural mechanisms of impulsive decision making, and have the potential to provide novel insight into the cocaine addiction prevention and treatment.

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Poster

825. Decision Making: Neuropharmacology

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Topic: F.03. Motivation and Emotion

Support: NIH Grant DA029421

NIH Grant DA036534

Univ of Florida Internal Funds

Title: Evaluating the role of striatal dopamine D2, glutamate mGluR5, and adenosine A2a receptor interactions in a rat model of risky decision-making

Authors: C. M. GOBIN[1], C. A. ORSINI[2], B. SETLOW[2], *M. SCHWENDT[1];
[1]Psychology, [2]Psychiatry, Univ. of Florida, Gainesville, FL

Abstract: Abnormal risky decision-making is a common feature in many psychiatric disorders, including addiction and ADHD, in which it may worsen prognosis and complicate treatment. Using a rodent model of risky decision-making, we have previously shown that decreased expression of dopamine D2 receptor (D2R) mRNA in the striatum is associated with elevated risky choice, and further, that administration of D2R agonists reduces risky choice. However, prolonged administration of D2R agonists may not be the most optimal treatment for abnormal risky decision-making, as it may produce a variety of side-effects, or even paradoxically promote risky choice in susceptible subjects. Since in the striatum, glutamate mGluR5 and adenosine A2a receptors display inhibitory synergistic control over D2R function, blockade of mGluR5 and/or A2a receptors may provide an alternative to dopaminergic treatments for maladaptive risk-taking behavior. In the current study we used a rat model of risky decision-making to investigate (1) whether the expression of A2a, mGluR5, and D2 receptors in specific striatal subregions correlates with risk-taking behavior, and (2) whether mGluR5 and A2a antagonists attenuate risk-taking or potentiate the effects of D2 agonists on risk-taking. In the risky decision-making task, rats made discrete-trial choices between two response levers, one which resulted in delivery of a small, “safe” food reward, and the other which resulted in delivery of a large, “risky” food reward accompanied by a variable probability of a mild footshock. Following characterization of performance in this task, rats were left undisturbed in their home cages for 1 week, followed by sacrifice and removal of brain tissue for immunoblotting analysis. Initial data from the dorsal striatum indicate the presence of a positive correlation between risk-taking (percent choice of the large, risky reward) and A2a receptor expression, and a negative correlation between risk-taking and Galpha-i protein expression. Ongoing studies are aimed at further characterization of D2-mGluR5-A2a functional synergism in the striatum in relation to risky decision-making behavior.

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Poster

826. Technology Development: DNA and Protein Imaging

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 826.01/CC46

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: NS-080687

MH-106245

EPS-1002410

Puerto Rico Science Technology and Research Trust Agreement No: 2013-000034

Title: Silver-graphene dots as nanoscale imaging probes for correlative optical and electron microscopy

Authors: C. SANTIAGO-ROBLES+[1], K. HABIBA+[2,3], I. I. TORRES-VAZQUEZ+[1], N. MARTINEZ-RIVERA[1], J. L. SERRANO-VELEZ[1], V. I. MAKAROV[2,3], G. MORELL[2,3], B. R. WEINER[2,4], R. D. POWELL[5], V. JOSHI[5], *E. ROSA-MOLINAR[1,2,6];
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Abstract: Major advances in cell biology and neuroscience have been made possible by new imaging instrumentation and the concomitant development of appropriate probes. Optical and electron based imaging instruments extend detection capabilities to the nanoscale level, but new nanoscale probes are needed to take advantage of the increased resolution. Graphene dots (GDs), 0D nanostructures of sp2 C in the 2-20 nm size range, show intrinsic fluorescence due to quantum confinement, surface defects, and edge structures and have attracted tremendous attention for their potential in cellular sensing and imaging. However, that potential has not been realized. A strategy to enhance the fluorescence quantum yield of GDs is by plasmonic interaction with metallic nanoparticles, most typically silver or gold. The proximity of a metallic nanoparticle to a fluorophore increases the local electromagnetic radiation intensity and the probability of spontaneously emitted photons. Therefore, the fluorescence of GDs can be increased by direct contact with metallic nanoparticles, in this case, silver nanoparticles. In our study, the silver-nanoparticle-augmented GDs show the utility of the silver-graphene dots (Ag-GDs) as a nanoscale imaging probe. Three-dimensional correlative imaging shows internally localized clusters of Ag-GDs within the somas and axons of spinal motor neurons following retrograde neural tract-tracing. New nanoscale imaging probes such as the one described here are needed to overcome the challenges of new optical and electron based imaging technologies and to take advantage of the increased resolution they provide. [+]contributed equally to the work presented

Disclosures: C. Santiago-Robles+: None. **K. Habiba+:** None. **I.I. Torres-Vazquez+:** None. **N. Martinez-Rivera:** None. **J.L. Serrano-Velez:** None. **V.I. Makarov:** None. **G. Morell:** None. **B.R. Weiner:** None. **R.D. Powell:** None. **V. Joshi:** None. **E. Rosa-Molinar:** None.

Poster

826. Technology Development: DNA and Protein Imaging

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 826.03/CC48

Topic: G.03. Staining, Tracing, and Imaging Techniques

Title: Visualization of myelin during development using black gold two

Authors: *R. A. DEYO[1], M. D. ALLEN[2], K. J. NELSON[2];
[1]Psychology, [2]Chem., Winona State Univ., Winona, MN

Abstract: Our goal was to create a histological atlas of myelin in the developing mouse brain for use in the study of disorders associated with abnormal myelination. The problem has been that myelin stains tend to be unreliable, of poor quality and can be difficult to use. Black-Gold II is a halogen gold phosphate complex with improved myelin staining properties relative to earlier Black-Gold and gold chloride methods (Schmued et al., *Brain Res*, 2008,1229: 210-7). In this study we used Black Gold II staining to track the development of myelin from the perinatal period through late adolescence in the C57BL6J mouse. All procedures followed the policies of the Society for Neuroscience for the use of animals in neuroscience research and the project was approved by the WSU IACUC. Male and female C57BL6J mice were removed from their litters on day 5, 10, 15, 20, 25, 28, or 60 post-partum and their brains were removed and fixed in 3% buffered formalin for at least 10 days prior to thin-sectioning at 40 microns. Sections were obtained in both the coronal and sagittal planes. Tissues were mounted on gelatin-subbed slides and stored at 4 c until stained. Animals from each age group were counterbalanced in each staining run to ensure that staining variables were kept to a minimum. The staining protocol followed that of Schmued et al. (2008). After staining and coverslipping, the slides were photographed and the resulting images were analyzed using NIH image-J software to determine the density of myelin staining. Myelin was visible at all ages, albeit faintly in ages younger than day 15 postpartum (see Figure 1). Myelin staining appears to peak by day 28 in C57BL6J male mice. These data demonstrate that the Black-Gold II stain can be used effectively to study postnatal myelination in mice and should prove to be a useful tool for the study of developmental disorders associated with abnormal myelination.

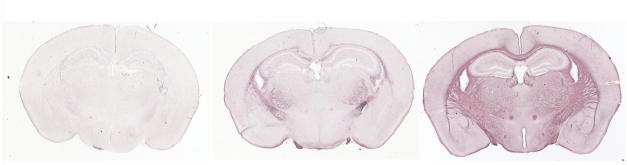

Figure 1

Disclosures: **R.A. Deyo:** None. **M.D. Allen:** None. **K.J. Nelson:** None.

Poster

826. Technology Development: DNA and Protein Imaging

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: NSF IGERT in Neuroengineering

NSF BRAIN EAGER CBET 14-50829

NSF CBET 14-03660

Beckman Institute Seed Grant

Title: Coherent quantum control in fluorescent dyes and caged neurotransmitter compounds by femtosecond pulse shaping

Authors: *E. D. ARK[1,2,3], S. YOU[3,4], H. TU[3], S. A. BOPPART[1,2,3,4];
[1]Electrical and Computer Engin., [2]Col. of Med., [3]Beckman Inst. for Advanced Sci. and Technol., [4]Bioengineering, Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: Caged neurotransmitter compounds and fluorescent dyes have been fundamental tools in the optical control and imaging of neural networks. In particular, multi-photon events with the use of pulsed laser sources have been favored for their reduced scattering and phototoxicity in tissue, as well as for the tighter spatiotemporal localization of transition events. The use of multiple optical stimulation or recording probes simultaneously would open the way to greater flexibility in experimental design. Unfortunately, due to factors such as the heterogeneity of the chemical environment in biological samples, there is a great deal of broadening of the absorption and emission spectra of these molecules. As a result, the use of multiple probes simultaneously often runs a significant risk of cross-excitation, even in the case of large separation in peak

sensitivities. The field of coherent control is concerned with exploiting quantum interference to guide a quantum system into a desired state. One way to achieve this is through the use of ultrafast pulse shaping to control the temporal profile of an applied electromagnetic field on time scales of the order of femtoseconds. Coherent control has been shown to afford experimenters the ability to alter the probability of multi-photon transition events by exclusively altering the spectral phase function of light, while leaving the spectral composition of the light intact. This leads to the possibility of improving the selectivity with which multiple optical probes present simultaneously within a sample can be activated by a shared light source. However, there has yet to be a systematic exploration of the potential contrast enhancement between pairs of probes that such techniques can achieve. Here, we use a supercontinuum-generating photonic crystal fiber (NL-1050-NEG-1, NKT Photonics) pumped by a Yb:KYW laser (1040 nm center wavelength, 80 MHz repetition rate, HighQ) as a broadband, high-intensity, pulsed light source spanning 723 nm to 1300 nm, whose spectral phase function is modified by the use of a 640 pixel femtosecond pulse shaper (MIIPSBox 640, Biophotonics Solutions Inc.). We show results for multi-photon fluorescence as well as mass spectrometry analysis of photolysis products of multi-photon uncaging with varying temporal pulse profiles in several commonly used dyes and caged compounds.

Disclosures: **E.D. Ark:** None. **S. You:** None. **H. Tu:** None. **S.A. Boppart:** None.

Poster

826. Technology Development: DNA and Protein Imaging

Location: Hall A

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Program#/Poster#: 826.05/CC50

Topic: G.03. Staining, Tracing, and Imaging Techniques

Title: Zinpyr-1 in flash frozen tissue can be used to show increased Zn fluorescence in the dentate gyrus and CA3 region of the hippocampus

Authors: *S. L. LIPPI, D. D. CERRI, J. M. FLINN;
Psychology, George Mason Univ., Fairfax, VA

Abstract: Zinc (Zn) is an essential element for development and biochemical processes including cell proliferation, enzymatic integration, and cellular communication. Although a majority of Zn within the body is bound through metalloproteins, metalloenzymes, and protein complexes, loosely bound or “free” Zn2+ can be detected through the use of fluorescent sensors including those in the Zinpyr family (Woodroofe, Masalha, Barnes, Frederickson, & Lippard, 2004). Although much research with Zn probes is conducted either in cell culture or *in vivo*,

Zinpyr-1 (ZP-1) can be applied histologically to freshly cut frozen brain tissue and analyzed in brain regions implicated in Zn signaling, such as the amygdala and the hippocampus (Frederickson & Bush, 2001). Zinpyr-1, a fluorescein-based sensor for Zn2+ (Woodroofe, et al., 2004) that stains bouton-Zn, was chosen for its membrane permeability, bright fluorescence, high Zn2+ affinity, and ideal excitation properties (Walkup, Burdette, Lippard, & Tsien, 2000). We have recently modified a standard protocol for ZP-1 staining in order to apply it to our histological studies. A 1mM stock solution of ZP-1 (Santa Cruz Biotechnology, Inc.) was made in DMSO and a working solution of 40μM was made through 0.9% saline. Brains from four-month old Sprague-Dawley rats were sliced coronally at 20μm on a Leica CM3050 S cryostat and placed on positively charged slides. Slices were exposed to ZP-1 for 30 minutes and then the ZP-1 was tilted off. Imaging was completed using an Olympus BX51 fluorescence microscope equipped with a fluorescein isothiocyanate (FITC) cube, and mercury burner. The FITC cube matched the recommended ZP-1 excitation and emission wavelengths of 490 nm and 530 nm, respectively. 1.25x and 2x objectives were used to capture images for further analysis through ImageJ (NIH). In agreement with previous research (Ketterman & Li, 2008) the hilus of the dentate gyrus and CA3 region exhibited the highest levels of fluorescence in the hippocampus.

Disclosures: **S.L. Lippi:** None. **D.D. Cerri:** None. **J.M. Flinn:** None.

Poster

826. Technology Development: DNA and Protein Imaging

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 826.06/CC51

Topic: G.03. Staining, Tracing, and Imaging Techniques

Title: Degeneration and normal neuron staining method to aid in quantitative analysis

Authors: ***B. TIPTON**, C. J. ZURHELLEN, H. T. YORK, J. A. BAUN, R. C. SWITZER, III; Lab., Neurosci. Associates, Knoxville, TN

Abstract: The Amino Cupric Silver (ACS) stain of deOlmos reveals neurons in the degenerative (disintegrating) state in the brain and spinal cord. These neurons stain intensely black, while normal neurons do not take up the stain. To assess the degree or the amount of degeneration, a numbered score (0,1,2,3,4, with 4 being highest level of degeneration) is usually assigned. Here we describe a more quantitative means for this type of evaluation that can be achieved by applying a second stain ‘over’ the ACS stain. The antibody NeuN reveals a marker expressed in all normal neurons over 2 weeks old. When combining the ACS stain with NeuN IHC on the same tissue, degenerative neurons stained with the ACS protocol can be counted against “live”

neurons that stain positive for NeuN. Using imaging software (FIJI) the numbers of degenerating (black) neuron and NeuN positive (brown) neurons can be determined for any given region of interest. Using 'batch processing' methods, captured images are pre-processed using Adobe Photoshop to make them more amenable for image analysis. Further batch processing using brightness, contrast, selection and thresholding tools, black degenerating neurons and brown "live" neurons are isolated for quantification using the 'particle analysis' tool in FIJI (Image J). Although this method does not replace quantitative determinations provided by the more time consuming and expensive Stereologic analysis, it does provide a numeric index of observables rather than a subjective assessment.

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Poster

826. Technology Development: DNA and Protein Imaging

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 826.07/CC52

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: NRF grant 2014-R1A1A2012804

Title: Development of novel sensors for autophagosome

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[1]Biol. Sci. and Biotech., Hannam Univ., Daejeon, Korea, Republic of; [2]Ecological Sci., Kyungpook Natl. Univ., Sangju, Korea, Republic of; [3]Kyungpook Natl. Univ., Sangju-si/gyeongsangbuk-Do, Korea, Republic of

Abstract: Autophagy,referred to as macroautophagy, is the intracellular bulky degradation pathwayin lysosome. Formation or degradation of autophagosome, a hallmark of autophagy, is critical for autophagic process. Therefore, monitoring of autophagosome is essential for autophagy research. However, so far, expression of GFP/RFP-LC3 is only way to detect autophagosome in living cells, which has the limitations due to overexpression of LC3. Here, we tried to develop new probes for autophagosome by monitoring endogenous LC3 using LC3-interacting region (LIR) motifs. To selectively detect LC3 in autophagosome embrane, a smallpeptide from *Aplysia* phosphodiesterase 4 (ApPDE4) short-form, which was necessary but not sufficient for membrane localization alone, was combined with a LIR motif from FYCO1. Newly generated probes could detect RFP-LC3-positive autophagosome in RFP-LC3

overexpressed MEF cells and cultured cortical neurons. Under starvation or rapamycin treatment, these probes could efficiently detect endogenous LC3-positive vacuoles in wild-type MEF but not in *atg5-/-* MEF cells, raising the possibility that these new probes might be used as specific markers for tracking endogenous LC3 positive autophagic vacuoles in living cells. We are currently modifying the newly generated probes to improve monitoring endogenous autophagosomes more efficiently in living cells.

Disclosures: **Y. Lee:** None. **Y. Jun:** None. **J. Lee:** None. **D. Jang:** None.

Poster

826. Technology Development: DNA and Protein Imaging

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 826.08/CC53

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: NSF STC EBICS CBET 0939511

NSF CBET 1040462

IBS-R020-D1

Title: Infrared diffraction phase microscopy for nanoscale imaging of live brain slices

Authors: ***E. MIN**[1,2], S. KIM[1], L. MA[3,1], W. JUNG[2,4], Y. WANG[1], G. POPESCU[1], C. BEST-POPESCU[1];
[1]Univ. of Illinois at Urbana-Champaign, Urbana, IL; [2]Ulsan Natl. Inst. of Sci. and Technol., Ulsan, Korea, Republic of; [3]Zhejiang Normal Univ., Jinhua, China; [4]Ctr. for Soft and Living Matter, Inst. of Basic Sci., Ulsan, Korea, Republic of

Abstract: Neuroimaging over broad spatial scales, molecule to organ, is key for answering fundamental questions about the connectivity of the brain. Histochemical stains and fluorescent labels remain the gold standard for differentiating various neuronal structures in the brain tissue. When imaging live cells and brain slices, fluorescent tags are often limited by photoxicity and photobleaching. Recently, label-free imaging has been considered as key for in neuroimaging. Therefore, optical imaging methods such as optical coherence tomography, optical projection tomography, spatial light interference microscopy (SLIM, Kim et al., Nature Photonics 2014, Mir et al., Sci. Rep. 2014), and diffraction phase microscopy (DPM, Park et al., PNAS 2010) that operate with intrinsic contrast has been introduced as valuable tools for neuroscience. DPM is particularly used to visualize neuronal network in wide field and detect fast nanoscale

fluctuations in cell membranes, due to its advantage of high speed and sensitivity. However, conventional DPM has been used with visible light mainly for thin specimens (e.g., single cell layers). As a result, penetration depth in thick tissue is limited due to visible light being scattered strongly. Here, we report on a new *label-free* approach for studying live brain slices with nanoscale sensitivity to morphology and dynamics. In order to push the applicability of DPM's label-free, nanoscale imaging to thick tissues, we developed a new instrument that uses common-path interferometry with near-infrared (NIR) light. Since the scattering mean free path of NIR is longer than that of visible light, we achieve a longer penetration depth without significant loss of transverse resolution. With NIR DPM, we demonstrate, for the first time to our knowledge, quantitative phase imaging of live mouse brain slices.

Disclosures: E. Min: None. **S. Kim:** None. **L. Ma:** None. **W. Jung:** None. **Y. Wang:** None. **G. Popescu:** None. **C. Best-Popescu:** None.

Poster

826. Technology Development: DNA and Protein Imaging

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Program#/Poster#: 826.09/CC54

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: Wyss PNM Platform grant

NIH 5U01MH106011-02

Title: A DNA based method for highly multiplexed and super-resolution imaging of neurons

Authors: *Y. WANG[1,2], S. S. AGASTI[1], N. DONOGHUE[1], R. JUNGMANN[3], P. YIN[1]; [1]Harvard Wyss Inst., Brookline, MA; [2]Program of Biol. and Biomed. Science, Harvard Med. Sch., Boston, MA; [3]Max Plank Inst. of Biochem. and LMU, Munich, Germany

Abstract: Fluorescence microscopy combined with various immunostaining methods allows us to visualize neurons directly. However, conventional fluorescence microscopy has limited capabilities in terms of resolving fine structural detail (i.e. low resolution) and multiplexed detection (i.e. ~4 targets in the same sample). This limits our ability to map key protein networks at high spatial resolution, for example, protein-protein interaction in individual synapses. Here, we describe a DNA based imaging method, named as Exchange-PAINT (Point Accumulation for Imaging in Nanoscale Topography), which offers high multiplexing power (>10x) and super-resolution (~10nm). Using Exchange-PAINT, we demonstrate here, for the first time, 8-target

super-resolution imaging in neurons. Additionally, by tuning the DNA length, Exchange-PAINT was adapted to a fast and robust multiplexed diffraction limited imaging. A 10-target image in neuron was achieved as fast as one hour. Exchange-PAINT utilizes transient binding properties of short DNA oligos (9nt) to achieve super-resolution in a highly multiplexed fashion. Specifically, fluorophore-conjugated DNA strands (i.e. imager Strand) transiently hybridize to the immobilized DNA docking strands on antibodies to accomplish the stochastic fluorescence blinking required for localization-based super-resolution microscopy. Importantly, since imager strands are not stably bound to their targets, they can be easily washed away using PBS. Orthogonal imager strands can therefore be sequentially applied to image an potentially infinite number of target proteins. Unlike other multiplexed immunostaining methods (e.g. array tomography), Exchange-PAINT allows each antibodies to be applied to the sample at the same time, thus dramatically reducing the total time required to perform such an experiment. To demonstrate the ability of Exchange-PAINT for super-resolution imaging, we selected 8 targets from neuron and astrocytes, of which 4 targets (alpha-tubulin, acetyl-tubulin, vimentin and Tom20) are structural proteins whereas the other 4 targets (bassoon, synapsin, gephyrin and vgat) are synaptic proteins. To adapt Exchange-PAINT for diffraction limited imaging, we increase the DNA length to 10nt and exposure time of cameras to a few second to capture all the binding events within a single frame of the image. We achieved diffraction limited imaging of 10 targets in neuron culture using a spinning disc microscope.

Disclosures: **Y. Wang:** A. Employment/Salary (full or part-time):; Harvard University. **S.S. Agasti:** None. **N. Donoghue:** None. **R. Jungmann:** None. **P. Yin:** None.

Poster

826. Technology Development: DNA and Protein Imaging

Location: Hall A

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Program#/Poster#: 826.10/CC55

Topic: G.03. Staining, Tracing, and Imaging Techniques

Title: Multiplexed immunofluorescence imaging and analysis of post-mortem human brain sections for the study of molecular phenotypes and neuropathological features

Authors: ***D. MEYER**[1], E. BAS[1], X. CHEN[1], D. V. DYLOV[1], Q. LI[1], C. LOWES[1], S. KAANUMALLE[1], M. E. MARINO[1], E. MCDONOUGH[1], A. SANTAMARIA-PANG[1], W. W. SEELEY[2], P. R. HOF[3];
[1]GE Global Res., Niskayuna, NY; [2]Univ. of California, San Francisco, San Francisco, CA; [3]Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Characterization of tissue by fluorescence microscopy is typically constrained by available excitation/emission channels, and consequently only a handful of markers can be simultaneously probed while retaining the spatial integrity of the tissue context. We have developed an approach to circumvent this problem using iterative rounds of staining, imaging and dye deactivation for molecular tissue characterization in cancer (Gerdes, 2013). In this work, we have extended the approach to brain tissue, allowing overlapping localization of dozens of cellular, structural and pathological markers. We validated more than 50 commercial antibodies against neuronal and immune markers as direct dye conjugates compatible with our process, and developed image processing and analysis algorithms for cellular and tissue analyses. Image processing includes multi-round image registration using DAPI-stained nuclei as tissue fiducials, correction of illumination non-uniformity, and removal of remaining autofluorescence signal by subtraction of paired images prior to staining. Image analysis employs a modular algorithm toolkit, allowing segmentation of channels, either singly or in combination, and quantification of signal intensity across all marker channels at the level of single cells, compartments or tissue structures. To demonstrate the potential of this approach, we conducted a 25-marker study of affected and non-affected brain regions from 9 Alzheimer's disease cases (Figure 1) and 4 non-AD controls, both in whole section and tissue array formats. Resulting images were segmented and quantitated for neurons and for microglia, enabling identification of cell subclasses via clustering of the expression profiles. This approach allows for thorough molecular, morphologic and spatial characterization of cell subclasses in relationship to each other and to pathological tissue features, and should be useful for the study of normative cell taxonomy and of molecular mechanisms in neurodegenerative disease. Reference: M.J. Gerdes, et al. Proc Natl Acad Sci USA 110:11982-7, (2013).

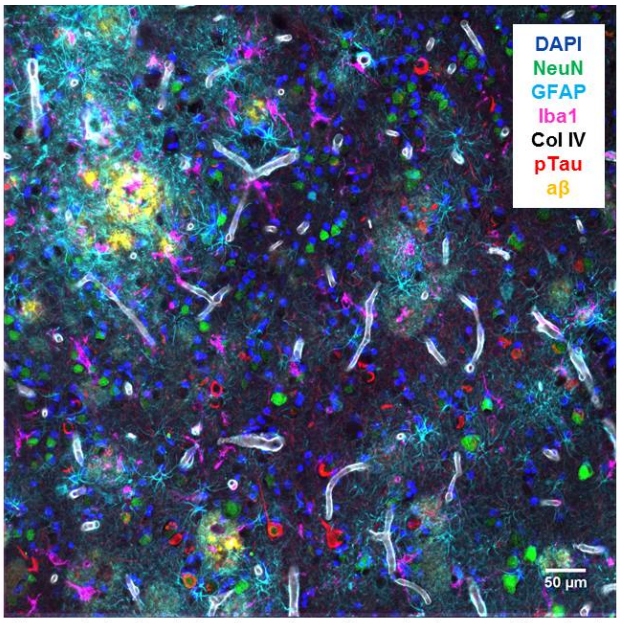

Figure 1. A subset of markers shown for cortex from an AD patient.

Disclosures: **D. Meyer:** A. Employment/Salary (full or part-time):; General Electric Company. **E. Bas:** A. Employment/Salary (full or part-time):; General Electric Company. **X. Chen:** A. Employment/Salary (full or part-time):; General Electric Company. **D.V. Dylov:** A. Employment/Salary (full or part-time):; General Electric Company. **Q. Li:** A. Employment/Salary (full or part-time):; General Electric Company. **C. Lowes:** A. Employment/Salary (full or part-time):; General Electric Company. **S. Kaanumalle:** A. Employment/Salary (full or part-time):; General Electric Company. **M.E. Marino:** A. Employment/Salary (full or part-time):; General Electric Company. **E. McDonough:** A. Employment/Salary (full or part-time):; General Electric Company. **A. Santamaria-Pang:** A. Employment/Salary (full or part-time):; General Electric Company. **W.W. Seeley:** F. Consulting Fees (e.g., advisory boards); Biogen-Idec. **P.R. Hof:** None.

Poster

826. Technology Development: DNA and Protein Imaging

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

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Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: Grant-in-Aid for JSPS Fellows (DC2) to W.L.

JSPS KAKENHI (25640015) to H.M.

MEXT KAKENHI (22115009, 15H01454, 15H04263) to T.I.

Title: Supernova systems enable high intensity single-cell labeling and labeled cell-specific gene-manipulation

Authors: *W. LUO[1,2], H. MIZUNO[1,2], R. IWATA[1,2], S. NAKAZAWA[1,2], T. IWASATO[1,2]; [1]Natl. Inst. of Genet., Mishima, Japan; [2]Dept. of Genet., Grad. Univ. for Advanced Studies (SOKENDAI), Mishima, Japan

Abstract: Methods that enable high intensity labeling of single cells and labeled cell-specific gene manipulation (e.g. knockout, knockdown, overexpression) are valuable for understanding cellular and molecular mechanisms responsible for development and function of the mammalian brains. For this purpose, we developed vector systems termed “Supernova”, which synergistically use the tTA/TRE expression system and site-directed recombination system (e.g. Cre/loxP) to enhance the expression of genes of interest only in a sparse population of cells. We recently reported the first version of Supernova method (Mizuno et al., Neuron 2014), in which

red fluorescent protein (RFP) was highly expressed in a small subset of cortical neurons by *in utero* electroporation (IUE)-mediated transfection of a Cre/loxP-based Supernova vector set. The whole cellular morphology including individual dendritic spines and axons were clearly visualized. RFP-labeled cell-specific gene knockout was also achieved when floxed mice were transfected. Combined with two-photon *in vivo* imaging, we successfully observed the dynamics of dendritic refinement of individual wild-type and mutant neurons in layer 4 of the neonatal mouse cortex (Mizuno et al., Neuron 2014). Here, we expanded the Supernova system in several aspects. First, we constructed Supernova vector sets that use different types of fluorescent proteins (e.g. GFP, CFP, GCaMPs, fluorescence proteins fused with subcellular localization signals). Second, we demonstrated that multiple genes can be co-expressed in individual cells. Third, we showed that other types of site-specific recombination systems (e.g. flpe/FRT, Dre/Rox) can also be used. Forth and finally, we showed that Supernova systems can be used for RNA interference. By expressing shRNA-based Supernova vectors in two distinct reporter mouse lines, we showed that expression of endogenous genes was suppressed. Thus, the Supernova systems provide powerful tools in various aspects of neuroscience, for elucidation of the neural properties and gene functions in single cell levels.

Disclosures: **W. Luo:** None. **H. Mizuno:** None. **R. Iwata:** None. **S. Nakazawa:** None. **T. Iwasato:** None.

Poster

826. Technology Development: DNA and Protein Imaging

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Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: CAS Grant Y422018202

Title: Combined structured-illumination with localization-based super-resolution microscopy

Authors: H. LI, X. JIN, Y. LIANG, S. LI, G. WEN, *H. JIA;
Brain Res. Instrument Innovation Ctr., Suzhou Inst. of Biomed. Engin. and Technol., Jiangsu, China

Abstract: Single Molecule localization based super-resolution microscopy methods, known as Photoactivated localization microscopy (PALM) and Stochastic Optical Reconstruction Microscopy (STORM), has gained much interests in biology due to its high spatial resolution down to 10 nm whilst using moderate laser power. However, its application to study the

dynamics process in live cells is limited by its slow image acquisition process. On the other hand, Structured Illumination Microscopy (SIM) can obtain video-rate imaging speed with worse spatial resolution. These limitation can be overcome by combining these two techniques together. Here, we describe an newly developed microscope system with such combination. Rapid physiological signals in live cells can be fist observed in the SIM mode, subsequently, small regions of interested can be selected for further high-resolution imaging with STORM mode.

Disclosures: **H. Li:** None. **X. Jin:** None. **Y. Liang:** None. **S. Li:** None. **G. Wen:** None. **H. Jia:** None.

Poster

826. Technology Development: DNA and Protein Imaging

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Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: NIH Grant NINDS 1R21NS078580

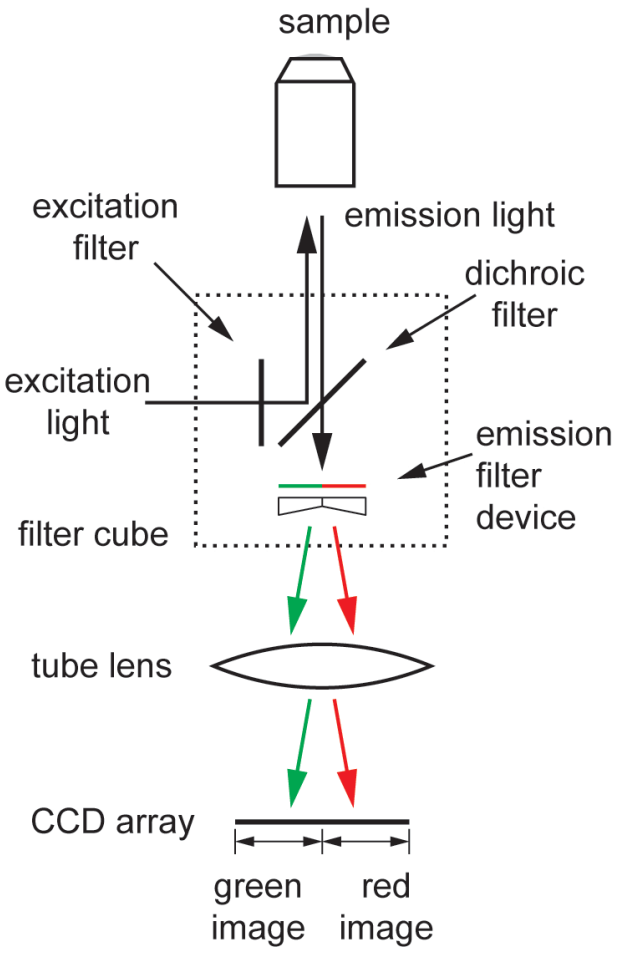
NIH Grant SBIR 1R43GM112403

Title: Wedge-based approach for simultaneous multichannel microscopy

Authors: S. H. CHUNG[1,3], *C. V. GABEL[2];
[1]Boston Univ. Sch. of Med., Boston University, MA; [2]Dept. of Physiol. and Biophysics, Boston Univ. Sch. of Med., Boston, MA; [3]Physical Sci. Inc, Andover, MA

Abstract: Multichannel (i.e., multicolor) microscopy is becoming increasingly relevant to many research areas; however, limitations to conventional approaches prevent full technique utilization. Our approach for simultaneous multichannel microscopy separates channels by a fundamentally different mechanism, leading to many advantages. The figure shows a schematic representation of a two-channel approach. Multiple sample fluorophores absorb multichannel excitation. Multichannel fluorescent emission passes through the dichroic and side-by-side emission filters, separating into parallel heterochromatic beamlets, which are the two channels. Wedges deflect the beamlets in opposite directions. The microscope tube lens images the channels on separate locations on the CCD for simultaneous observation. For typical CCD and tube lens focal lengths, the wedge angle is small, and chromatic dispersion negligible. The use of wedges rather than mirrors yields significant improvements in simplicity and user-friendliness

because errors propagate through mirror reflection different than wedge prism deflection. An error in mirror orientation changes both incident and reflected light angles, producing twice the error in the reflected beam direction. In contrast, for our wedges the error in the refracted beam direction is the error in wedge orientation multiplied by 0.0002, so wedge orientation errors have little impact on deflected beam direction. Thus, the use of wedges significantly reduces the need for precise alignment. This allows users to place our device in the standard filter wheel without complex installation and alignment. Our device is about 1/3rd the cost of existing commercial devices. We have developed multiple device prototypes and imaged *in vivo* neuronal calcium transients, with results comparable to a conventional dual-view device. In addition, we employed a four-channel device to efficiently image Brainbow samples. In summary, our simple, user-friendly, and inexpensive device allows single-channel microscopes to perform simultaneous multichannel microscopy.



Disclosures: **S.H. Chung:** None. **C.V. Gabel:** None.

Poster

827. Tracing and Imaging Methods

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Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: NIH Whole Mouse Brain 1U01MH105971

Title: Single neuron reconstruction using oblique plane tomography

Authors: *A. NARASIMHAN, K. UMADEVI VENKATARAJU, J. TUCCIARONE, Z. J. HUANG, D. F. ALBEANU, P. OSTEN;
Cold Spring Harbor Lab., Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: Understanding the connectivity of neuronal circuits with cellular resolution is paramount for uncovering the principles governing brain network organization and functional architecture. This complex circuitry is assembled using diverse populations of neurons. Recent advances provide handles to genetically target specific subsets of neurons and systematically trace their projections across the brain. We developed a custom dual color Oblique Plane Tomography (dcOPT) platform based on Digital Scanned Laser Light Sheet Microscopy (DLSM), in which the illumination and detection paths are oriented obliquely (45°) with respect to the tissue surface. dcOPT is an automated whole-brain imaging technique that uses the principle of DLSM where the sample is illuminated with a scanned micrometer thin laser beam to generate a planar light sheet and images are acquired by a fluorescence wide-field microscope placed perpendicular to the illumination path. The oblique orientation allows for imaging the brain surface to ~500 μm depth in an XY raster pattern. Once the raster scan is completed, the brain is translated to an integrated vibratome to section the imaged top 450 μm tissue morsel. The raster scan and automated sectioning is repeated iteratively to obtain whole brain coverage. Since tissue scattering limits the light penetration depth of light and increases imaging time, we further modified and optimized the CUBIC protocol for clearing brains (~ 10 days). The current instrument configuration represents a significant advance compared to previous reports, allowing the whole cleared adult mouse brain be imaged within ~10 hrs at 0.7 X 0.7 X 5 μm voxel resolution in 2,500,000 tiles with overlapping regions for image registration and reconstruction. For mapping and tracing neuronal projections of brains, we developed a custom atlas that warps onto the Allen Reference Atlas. We are using dcOPT to trace input and output projections from defined cell types of neocortex and piriform cortex. First, we present examples of single cell labeling of virally induced supragranular Chandelier cells, an enigmatic cell type that provides powerful inhibition at axon initial segment of pyramidal neurons. Second, via similar approaches, we characterize the projections patterns of subsets of supragranular pyramidal

neurons across the brain. These strategies enrich our understanding of cortical structure and connectivity and suggest roles for the subtypes of pyramids in information processing.

Disclosures: **A. Narasimhan:** None. **K. Umadevi Venkataraju:** None. **J. Tucciarone:** None. **Z.J. Huang:** None. **D.F. Albeanu:** None. **P. Osten:** None.

Poster

827. Tracing and Imaging Methods

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Program#/Poster#: 827.02/CC60

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: NSF Grant #1256086

NIH/NINDS Grant #1R01-NS54252

Title: Enhancing robustness of sectioning and imaging in knife-edge scanning microscopy

Authors: ***Y. CHOE**[1], D. E. MILLER[1], R. S. SHAH[1], W. ZHANG[1], J. YOO[1], D. MAYERICH[2], J. KWON[3], J. KEYSER[1], L. C. ABBOTT[1];
[1]Texas A&M Univ., College Station, TX; [2]Univ. of Houston, Houston, TX; [3]Kettering Univ., Flint, MI

Abstract: Advances in high-resolution 3D microscopy have enabled the investigation of subcellular microstructures in biological specimens. For higher resolution imaging of whole organs or even whole animals, an increasing number of techniques are relying on physical sectioning [1]. However, the physical sectioning imaging process is not without error. Common errors include imaging artifacts due to vibration of the knife (chatter), illumination irregularities, and obstruction due to debris generated from the sectioning process. However, these problems are not widely recognized and thus solutions are scarce. In this abstract, we present our effort to characterize, detect, and correct imaging error due to the sectioning process in the Knife-Edge Scanning Microscope (KESM) developed in our laboratory (Fig 1). KESM can image on the order of 1 cm^3 at sub-micrometer resolution (0.7 um lateral, 1.0 um axial) [2]. We present (1) methods to characterize the vibration of the knife using accelerometers, and correlating that with imaging artifacts due to chatter, (2) controlling low-amplitude, high-frequency vibration of the knife using piezoelectric oscillators to reduce chatter, and (3) imaging error detection and alert system [3] based on image change-detection. We applied these techniques to image whole

zebrafish embryos (Nissl-stained, Fig 2), and to detect errors automatically in our Nissl whole mouse brain data. Imaging and analysis results will be reported (Fig 3).

1. Choe, Y. Physical sectioning microscopy. In Dieter Jaeger and Ranu Jung, editors, Encyclopedia of Computational Neuroscience, pages 2376-2379. Springer, New York, 1st edition, 2015.
2. Mayerich, D., Abbott, L., & McCormick, B. (2008). Knife-edge scanning microscopy for imaging and reconstruction of three-dimensional anatomical structures of the mouse brain. J. of microscopy, 231(1), 134-143.
3. Zhang, W., Yoo, W., Keyser, J., Abbott, L. C., and Choe, Y. Real-time detection of imaging errors in the knife-edge scanning microscope through change detection. In Proc. of the IEEE Int'l Symp. on Biomed. Imaging, 2015.

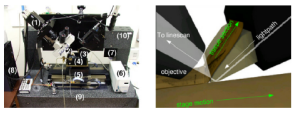

Fig. 1. Knife-Edge Scanning Microscope.

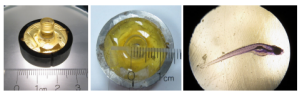

Fig. 2. Zebrafish Specimen Prepared for KESM Imaging.

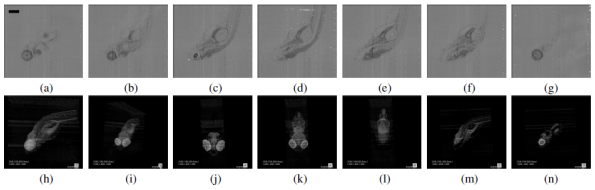

Fig. 3. KESM Zebrafish Image Data and 3D Visualization. Scale bar = 200 µm.

Disclosures: Y. Choe: None. **D.E. Miller:** A. Employment/Salary (full or part-time):; Capsher Technology. **R.S. Shah:** A. Employment/Salary (full or part-time):; FactSet. **W. Zhang:** A. Employment/Salary (full or part-time):; Amazon. **J. Yoo:** None. **D. Mayerich:** None. **J. Kwon:** None. **J. Keyser:** None. **L.C. Abbott:** None.

Poster

827. Tracing and Imaging Methods

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 827.03/CC61

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: NIH/NINDS #1R01-NS54252

NSF #0079874

NSF #1337983

Title: Internet enabled robotic microscope powered by knife-edge scanning microscopy

Authors: S. RAGHAVAN[1], Y. CHOE[2], D. MAYERICH[3], T. HUFFMAN[4], M. GOODMAN[4], C. DANIEL[4], *J. KWON[1];
[1]Electrical and Computer Engin., Kettering Univ., Flint, MI; [2]Texas A&M Univ., College Station, TX; [3]Electrical and Computer Engin., Univ. of Houston, Houston, TX; [4]3Scan, San Francisco, CA

Abstract: Scanning tissue samples at sub-micrometer resolution can help bridge the gap between slow but highly detailed electron microscopy and fast but less informative MR imaging. The imaging technique, Knife-Edge Scanning Microscopy (KESM) [1], allows us to scan a tissue block at high speed with sub-cellular level resolution. We implemented a scanning microscope powered by KESM and digitized a wide variety of organs [2]. However, the instrument had a few critical issues. The complex design required users to have extensive knowledge of machining and optics. This hindered its application as a shared-use instrument for research. Manual intervention for fixing operational problems caused misalignments in the imaging module. Remounting the tissue resulted in further misalignment as well as registration issues. We present the Internet Enabled RObotic Microscope (IEROM), the second generation of the microscope powered by KESM that solves the aforementioned problems. Advantages of the IEROM include 1/3 cost and ease of shared operation with a login based web interface control. The imaging module has been upgraded to use precision angle brackets to maintain the orientation required for line scan imaging. Magnetically pre-loaded kinematic sample holder helps rapid sample changes and easier user interface. Other improvements include illumination changes, higher sensitivity of line scan camera with a responsivity of more than 6 times that of original design and better positioning mechanics reduced scanner size to ¼ that of the original. The data resulting from the robust instrument, shared on an open virtual microscope platform, is expected to accelerate discovery in neuroscience. References: [1] Mayerich, D., Abbott, L. C., and McCormick, B. H. (2008). Knife-edge scanning microscopy for imaging and reconstruction of three-dimensional anatomical structures of the mouse brain. Journal of Microscopy, 231:134-143. [2] Chung, J. R., Sung, C., Mayerich, D., Kwon, J., Miller, D. E., Huffman, T., Abbott, L. C., Keyser, J., and Choe, Y. (2011). Multiscale exploration of mouse brain microstructures using the knife-edge scanning microscope brain atlas. Frontiers in Neuroinformatics, 5:29.

Disclosures: S. Raghavan: None. **Y. Choe:** None. **D. Mayerich:** None. **T. Huffman:** None. **M. Goodman:** None. **C. Daniel:** None. **J. Kwon:** None.

Poster

827. Tracing and Imaging Methods

Location: Hall A

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Program#/Poster#: 827.04/CC62

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: NYSTEMC029157

Title: Labeling and mapping memory traces in intact mouse brains of control and disease states

Authors: *I. PAVLOVA[1,3], S. C. SHIPLEY[1], R. HEN[2,3], C. A. DENNY[2,3];
[2]Psychiatry, [1]Columbia Univ., New York, NY; [3]Integrative Neurosci., Res. Fndn. for Mental Hygiene, Inc., New York, NY

Abstract: Visualizing behaviorally-evoked neural activity maps in intact mouse brains is essential in studying circuit-based mechanisms underlying learning and memory. Here, we compare methods for obtaining whole brain maps of markers for neural activity during memory encoding and/or memory retrieval based on intact tissue clearing, immunolabeling or endogenous transgenic expression of fluorophores, and automated microscopy imaging and analysis. Specifically, we utilized an ArcCreERT2 transgenic mouse model that allows for the indelible labeling of neurons that encode individual memory traces and outline a protocol based on organic solvent clearing and immunolabeling for markers, such as: eYFP, c-Fos and Arc. We also outline a method for the automatic microscopic imaging. In summary, we demonstrate that these methods allows for uniform labeling of memory traces across the brain in less than 18 days and present whole brain maps of memory traces in normal mice and mouse models of disease states.

Disclosures: I. Pavlova: None. **S.C. Shipley:** None. **R. Hen:** None. **C.A. Denny:** None.

Poster

827. Tracing and Imaging Methods

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 827.05/CC63

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: Grants-in-Aid for Scientific Research on Innovative Areas (#26119502)

Title: Rabies virus vector with improved transgene expression level for transsynaptic tracing

Authors: *Y. SOTA, S. OHARA, S. SATO, K. ITO, K.-I. TSUTSUI, T. IIJIMA;
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Abstract: Recombinant viral vectors that can cross synapses and can strongly express foreign genes are useful for investigating the organization of neural circuits. We have previously developed a recombinant rabies virus (RV) vector based on an attenuated HEP-Flury strain in which the CVS strain glycoprotein (CVSG) takes the place of the HEP-Flury strain glycoprotein (HEPG). This vector (rHEP5.0-CVSG) can be used as a transsynaptic tracer because it selectively infects neurons and propagates between synaptically connected neurons in a retrograde direction. Its relatively low level of transgene expression, however, makes immunohistochemical staining necessary if one wants to visualize the morphological features of the infected neurons. This vector therefore isn't suitable for use with marker proteins that cannot be immunostained. To develop a recombinant RV vector with a high level of transgene expression, in this study we focused on two viral proteins: RNA polymerase (L) and glycoprotein (G). We first attempted to increase the expression of the L gene because increased L-gene expression level is known to enhance viral mRNA transcription. An L-gene-enhanced RV vector (rHEP5.0-CVSGctL) was constructed by shortening the intergenic region between G and L gene from 24-nucleotide to 2-nucleotide. Next, we modified the G of the RV. We recently reported that the expression of the G gene also has an influence on the transgene expression level of the RV vector. To enhance the interaction of the CVS-derived G with the matrix protein of HEP-Flury strain, we constructed a G-modified RV vector (rHEP5.0-CVSG-HEPGCD) by replacing the cytoplasmic domain of CVSG with that of HEPG. These modifications improved the transgene expression level of the RV vector, which was examined by measuring the mRFP fluorescence intensity expressed by the vector. To further evaluate the usability of this RV vector, we constructed an RV vector that expresses a genetically encoded fluorescent timer (FT). The FT was an mCherry-derived monomeric variant that changed its fluorescence from blue to red over time. By using this high-transgene-expression RV vector, we succeeded in visualizing the infected neurons with the FT fluorescence *in vivo* without any staining. Furthermore, the primary infected neurons could be distinguished from the secondary infected neurons by the difference of the fluorescence wavelength. We expect this improved RV vector to be useful in revealing the hierarchical connectivity of the central nervous system.

Disclosures: Y. Sota: None. **S. Ohara:** None. **S. Sato:** None. **K. Ito:** None. **K. Tsutsui:** None. **T. Iijima:** None.

Poster

827. Tracing and Imaging Methods

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 827.06/CC64

Topic: G.03. Staining, Tracing, and Imaging Techniques

Title: Differential collateral patterns of sensory corticofugal projection neurons revealed by target-specific AAV2/1-mediated retrograde tagging

Authors: *B. ZINGG[1], L. MESIK[2], X.-Y. JI[2], H. TAO[2], L. ZHANG[2];
[1]Neurosci. Grad. Program, USC, Los Angeles, CA; [2]Zilkha Neurogenetic Institute, USC, Los Angeles, CA

Abstract: Projection neurons form long range connections that give rise to large-scale networks in the brain. In the cortex, neuronal populations with distinct laminar distributions form specific connections with cortical and subcortical targets. The degree to which these populations overlap in their targeting--or represent independent output channels--is uncertain, as is their functional contribution to cortical processing. Currently, experimental access to these cell groups is hindered by a limited number of transgenic mouse lines and the feasibility of optogenetically manipulating axonal target terminals. Furthermore, viruses currently available for retrograde labeling of projection neurons have limited functional use due to toxicity or inefficiency. Here we present a method for accessing projection neuron subtypes using two commercially available adeno-associated viruses (AAVs). This method allows for the selective labeling of neurons defined by their projection target and reveals all additional collateral targets for the population. Using this approach we find that different corticofugal populations in primary auditory or visual cortex exhibit partially overlapping, yet distinct, collateralization profiles. Moreover, this method may provide a means for long term, non-toxic, retrograde expression of opsins or calcium indicators for use in functional studies in these projection-defined neurons.

Disclosures: B. Zingg: None. **L. Mesik:** None. **X. Ji:** None. **H. Tao:** None. **L. Zhang:** None.

Poster

827. Tracing and Imaging Methods

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 827.07/CC65

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: The Whitehall Foundation

Title: Novel strategy for studying the circuit organization of globus pallidus in cell type and projection specific manner

Authors: V. LILASCHAROEN, S. SHIN, D. KNOWLAND, *B. LIM;
Biol. Sci., UCSD, La Jolla, CA

Abstract: The brain is an enormous network consists of numerous neuronal cell types, which are organized into distinct elaborate circuits that give rise to such a diverse array of functions. Understanding how these neural circuits underlie perception, cognition and behavior is a major goal of neuroscience research. The extreme complexity of the brain is one of the main difficulties that hinder our understanding of the organization of these circuits and how the dysregulation of circuits contributes to psychiatric illness. Recent advances in circuit tracing have provided powerful tools that reveal extensive information about the neural circuitry. However, thus far, no viral tracer has proven potent enough to allow a robust, long-lasting retrograde expression of transgenes without inducing cytotoxicity. Because even neighboring neurons of the same cell type differ in their connectivity and functions, a new method is required to achieve both cell-type- and projection-specific delivery of transgene via retrograde infection. Here we present a new viral strategy that allows long-term expression of transgenes including optogenetic tools and neural activity sensors in a cell-type- and projection-specific manner. We developed a novel viral vector based on the rabies glycoprotein-pseudotyped equine infectious anemia virus (EIAV), which has been proven successful to infect neurons retrogradely. We genetically engineered this EIAV vector to express site-specific recombinase including Flp, Dre and VCre in a Cre-dependent manner. Together with adeno-associated virus (AAV) expressing transgenes such as fluorescent markers, opsins, and genetically encoded calcium indicators in a Flp-, Dre- or VCre-dependent manner, we are able to deliver these transgenes in a specific population within the same cell type of neuron that projects to an area of interest. We will demonstrate the application of this strategy by dissecting the circuit of the external segment of the globus pallidus (GPe). GPe is one of the major nuclei of the basal ganglia that involves in motor learning, habit formation and is thought to contribute prominently to basal ganglia dysfunction in Parkinson's diseases. In fact, GPe is the one of major targets for deep brain stimulation for alleviating dyskinesia, dystonia, and symptoms of PD. However, the anatomical organization of GPe circuitry including cell types, efferent and afferent connections and their roles in pathological symptoms have not been fully addressed. By using this strategy, together with transgenic mice, we will be able to delineate the inputs and outputs relationship and projection-specific roles of different distinct neuronal cell types of GPe.

Disclosures: V. Lilascharoen: None. **S. Shin:** None. **D. Knowland:** None. **B. Lim:** None.

Poster

827. Tracing and Imaging Methods

Location: Hall A

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Program#/Poster#: 827.08/CC66

Topic: C.17. Drugs of Abuse and Addiction

Support: T32 AA007474

R37 AA009986

P50 AA010761

Title: Using the G-deficient recombinant rabies virus to study multi-synaptic fronto-cerebellar circuitry

Authors: *P. A. ZAMUDIO-BULCOCK, J. J. WOODWARD;
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Abstract: The envelope protein G (RG)-deficient rabies virus (RVΔG) was developed to trace monosynaptically connected neuronal circuits. But, its efficiency at labeling fine dendrite structures, and its low neurotoxicity (i.e. unchanged electrophysiological properties in infected neurons), also makes it an attractive candidate for morphological and functional studies of neuronal connectivity. In these viral vectors, the RG coding sequence is replaced with that of a reporter protein such as mCherry that permits infected cells to be visualized. In addition, the virus has the envelope glycoprotein from the avian sarcoma and leucosis virus (EnvA) that is not recognized by mammalian neurons. Thus, infection and generation of new viral particles is limited to cells expressing RG and the receptor for EnvA, receptor Tumor Virus A (TVA), that can be provided by using AAV expression vectors. Source cells infected with all components result in effective monosynaptic labeling of connected neurons. Since AAV viruses do not undergo significant retrograde or transynaptic transport, the newly generated RVΔG in the connected neuron cannot cross another synapse. In these studies, we surmounted this restriction via AAV delivery of RG in a relay region between the frontal cortex and the cerebellum, thus permitting an additional monosynaptic crossing of the RVΔG. This allowed us to identify individual neurons within the frontal cortex that sent disynaptic projections into the cerebellar cortex (CBC) via the pons (PN). First, AAV viruses containing RG and TVA were injected into CBC L7; and GFP- labeled AAV-RG was delivered into the PN. These viruses were allowed to express for 2 weeks. Subsequently, RVΔG-EnvA was injected into CBC L7, using the same coordinates where the TVA and RG AAVs had been injected. After 10 days, slices were prepared and analyzed for RVΔG - mCherry fluorescence. The CBC L7 received dense monosynaptic projections from the rostral portion of the PN and the caudal portion of the inferior olive. In the medial portion of the PN there was an overlap between RG-AAV and RVΔG expression, where source cells expressing both viruses were identified. Consequently, RVΔG-expressing neurons were found in layer V of the frontal cortex, predominantly in the motor centers, M1 and M2. Together with results from preliminary studies of dendrite morphology and electrophysiological recordings, these studies indicate that RVΔG can be used to study

anatomical, morphological and functional properties of fronto-cerebellar connections. Supported by T32 AA007474, R37 AA009986 and P50 AA010761.

Disclosures: P.A. Zamudio-Bulcock: None. **J.J. Woodward:** None.

Poster

827. Tracing and Imaging Methods

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Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: NIH Grant R01NS057476

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NIH Grant R01EB000790

NIH Grant R01HL081273

NIH Grant R01EB007279

AHA Grant SDG7600037

Title: Facilitating the adoption of oxygen partial pressure imaging with two-photon microscopy

Authors: *S. SAKADZIC[1], T. V. ESIPOVA[2], S. A. VINOGRADOV[2], D. A. BOAS[1];
[1]Massachusetts Gen. Hosp., Charlestown, MA; [2]Univ. of Pennsylvania, Philadelphia, PA

Abstract: The assessment of brain oxygenation on the microscopic level has the potential to transform our understanding of important clinical problems, such as stroke, Alzheimer's disease, dementia, chronic hypertension, and brain cancer, facilitating the development of new therapies and helping to improve clinical imaging and treatment protocols. Until now, no technology has been capable of microscopic oxygen imaging in the brain with high spatial and temporal resolution. Over the past several years we have developed a method, termed two-photon phosphorescence lifetime microscopy of oxygen (2PLM), which has the unique capability of fulfilling this niche. This is the only imaging method that allows high resolution mapping of brain oxygenation in real time. 2PLM of oxygen is a combination of state-of-the-art two-photon enhanced phosphorescent probes and a unique variant of two-photon laser scanning microscopy -

both of which are not presently available commercially. The transformative power of 2PLM of oxygen has been demonstrated in several high-impact publications [1-7], producing great interest in the neuroscience community. We are aiming to set up a self-sustaining resource that will promote widespread use of the two-photon oxygen imaging technology, making this new powerful method available to a broad group of neuroscience researchers. 1. Devor, A., Sakadžić, S., Saisan et al. “Overshoot” of O2 Is Required to Maintain Baseline Tissue Oxygenation at Locations Distal to Blood Vessels. J. Neurosci. 31, 13676-13681 (2011). 2. Gagnon, L., Sakadžić, S., Lesage et al. Quantifying the Microvascular Origin of BOLD-fMRI from First Principles with Two-Photon Microscopy and an Oxygen-Sensitive Nanoprobe. J. Neurosci. 35, 3663-3675 (2015). 3. Lecoq, J., Parpaleix, A., Roussakis et al. Simultaneous two-photon imaging of oxygen and blood flow in deep cerebral vessels. Nat. Med. 17, 893-898 (2011). 4. Parpaleix, A., Houssen, Y.G., Charpak, S. Imaging local neuronal activity by monitoring PO2 transients in capillaries. Nat. Med. 19, 241-246 (2013). 5. Sakadžić, S., Mandeville, E.T., Gagnon et al. Large arteriolar component of oxygen delivery implies a safe margin of oxygen supply to cerebral tissue. Nat. Commun. 5, 5734 (2014). 6. Sakadžić, S., Roussakis, E., Yaseen, M.A. et al. Two-photon high-resolution measurement of partial pressure of oxygen in cerebral vasculature and tissue. Nat. Methods 7, 755-759 (2010). 7. Spencer, J.A., Ferraro, F., Roussakis et al. Direct measurement of local oxygen concentration in the bone marrow of live animals. Nature 508, 269-273 (2014).

Disclosures: **S. Sakadzic:** None. **T.V. Esipova:** None. **S.A. Vinogradov:** None. **D.A. Boas:** None.

Poster

827. Tracing and Imaging Methods

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 827.10/CC68

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: NIH DP2 MH100008

Title: Trans-cellular activation of transcription for visualization of neural circuits

Authors: ***J. BONKOWSKY**, J. GAO, M. KEEFE, T. STEVENSON;
Dept. of Pediatrics, Univ. of Utah Sch. of Med., Salt Lake City, UT

Abstract: Visualization and manipulation of neural circuitry has remained a vexing problem in neuroscience. Our goal is to translate and implement a novel methodology, trans-cellular

activation of transcription (TCAT), to both genetically label cell-cell interactions, as well as to induce gene expression in interacting cells to assemble a functional circuit map of connectivity during development. TCAT is based on components from the receptor/ligand pair of Notch/Delta. Upon ligand binding to receptor, the intracellular domain of Notch is cleaved and translocates to the nucleus. We replaced the intracellular domain of Notch with the yeast transcriptional activator Gal4, so that we can express transgenes at the Gal4-binding site UAS. For TCAT we used the homologs LAG-2 (Delta) and LIN-12 (Notch) from the nematode *C. elegans* to prevent cross-reactivity with the endogenous zebrafish proteins. We overcame species-incompatibility of the protease cleavage reaction necessary for TCAT by developing a chimeric system: receptor-ligand binding specificity is maintained using *C. elegans* LAG-2 and LIN-12 binding domains, but with substitution of the zebrafish Delta and Notch signal sequences and transmembrane domains. In proof-of-principle experiments, we found that chimeric LAG-2/Delta tagged with red fluorescent protein (LADR) and LIN-12/Notch (LINch) activates transcription in different cell types in transient injections. To demonstrate the wide applicability of TCAT for a range of biological questions we have generated constructs expressing LINch or LADR in different cell types including retinal ganglion cells, dermal progenitor cells, epidermal cells, and in different neuron sub-types. TCAT can be used to drive expression of any desired gene; the method allows both labeling and manipulation in a variety of biological systems. We anticipate that TCAT may represent a significant technical innovation for mapping and understanding brain circuits in zebrafish and other vertebrate systems.

Disclosures: **J. Bonkowsky:** None. **J. Gao:** None. **M. Keefe:** None. **T. Stevenson:** None.

Poster

827. Tracing and Imaging Methods

Location: Hall A

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Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: NIH NS045193

P40 RR 018604

Pew Fellowship in the Biomedical Sciences 2010-000225-002

NRSA 1F31NS089303-01A1

Princeton Neuroscience Institute Innovation Fund Award

NIH BRAIN U01 NS090541

Nancy Lurie Marks Family Foundation

Title: Mapping of posterior cerebellum to thalamic and neocortical targets using herpesvirus-based anterograde tracers and large-scale tissue clearing

Authors: T. J. PISANO[1], T. K. WEIGEL[1], E. A. ENGEL[1], S. DEIVASIGAMANI[1], L. A. LYNCH[1], L. W. ENQUIST[1], *S. S.-H. WANG[2];
[1]Neurosci. Inst. and Dept. of Mol. Biol., [2]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: The cerebellum sends information to specific targets throughout the brain using closed loops as a major structural motif, in which a given cerebellar region shares reciprocal connections with specific target regions throughout the neocortex. However, this topographic relationship has been poorly characterized, in part because pathways in both directions are polysynaptic. To trace ascending cerebellum-to-neocortex pathways, we used H129 strains of herpes simplex virus 1 (HSV1-H129), which cross synapses and move largely anterogradely (Wojaczynski et al., 2014. Brain Structure and Function. 1-26). We made injections of HSV-H129 (2.8x104 to 5.6x104 PFUs) at a range of locations in lobule VI. Coinjection with Cholera Toxin B revealed that injection sites were 0.45-1.5 mm wide. After injection of HSV1-H129 768 (CMV-Brainbow 1.0L), we sectioned the brain after 3-5 days and found dTomato expression in thalamic and cortical regions. We found expression in two regions known to be required for cognitive flexibility, the parafascicular nucleus of thalamus (Brown et al., 2010. J. Neurosci. 3043:14390-14398) and the anterior cingulate cortex. Patterns of maximal expression varied across animals, indicating the potential to map projection topography. We are now using iDISCO (Renier et al., 2014. Cell. 159.4:896-910) to clear volumes of tissue, and imaging with a light-sheet fluorescence microscope. After clearing, HSV-labeled neurons visualized by immunohistochemistry are bright enough to allow detection throughout the entire mediolateral depth of a sagittally cut half brain, a distance of 4 mm. This approach opens the possibility to reconstruct cerebello-thalamo-neocortical projection patterns on large scales without need for tissue sectioning. We are now combining these methods with Cre-based recombination to label specific routes, such as paths that pass through dopaminergic neurons.

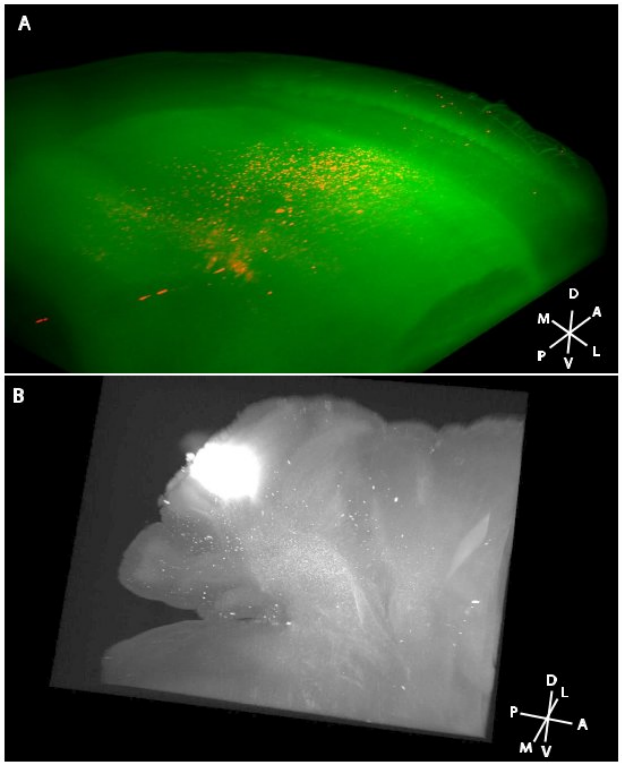

Figure: Labeling of neurons in iDISCO-cleared tissue after injection of HSV-H129-Brainbow 1.0L. (A) Neocortex. Red dots indicate dTomato-positive neurons. The green image indicates autofluorescence. (B) Injection site in cerebellum lobule VI, labeled with CTB.

Disclosures: **T.J. Pisano:** None. **T.K. Weigel:** None. **E.A. Engel:** None. **S. Deivasigamani:** None. **L.A. Lynch:** None. **L.W. Enquist:** None. **S.S. Wang:** None.

Poster

827. Tracing and Imaging Methods

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 827.12/CC70

Topic: G.03. Staining, Tracing, and Imaging Techniques

Title: *In vitro* patterning of neural circuits at single cell resolution via optical tweezers

Authors: *B. POLAT[1], S. BAY[2], G. OZTURK[1];
[1]Regenerative and Restorative Med. Res. Ctr. (REMER), Istanbul Medipol Univ., Istanbul, Turkey; [2]Mol. Biol. and Genet., Gebze Tech. Univ., Kocaeli, Turkey

Abstract: Optical tweezers trap and manipulate microscopic objects via highly focused laser beam.With simple adjustments this tool can be facilitated in cell culture for various experimental

purposes. Good examples to these can be combining cells, delivering packed agents to cells and to recreating neuronal networks with intended topology and hierarchy. In this study we used optical tweezers as a simple and effective tool to trap and carry large primary neurons in designated patterns for long term monitoring of network structure and function. For this purpose, dorsal root ganglia cells were dissociated and neurons were selectively isolated via gradient centrifuge technique among a mixed cell population. Dorsal ganglia neurons are large and heavy by nature which makes them hard to pick up and manipulate once they settle down. So islands of thin silicon elastomere layers were produced to avoid the quick adhesion of neurons to the petri dish. This delayed the unwanted adherence up to 1 hour and gave us sufficient time for cell manipulation. Freshly prepared 50 cells per 5µl were plated onto the non adhesive silicone island, and cells were trapped and carried to the laminin coated network area. The optical tweezer tool facilitated a 1W continious wave diode laser of 1064 nm wavelength via a high numerical apperture, low magnification water immersion objective (**32x/0.85**) for laser tweezing. As a result, cells up to 30 µm diameter were succesfully carried up to 600 um distance. About 75% power was sufficient for glass surface while the silicone coated area called for power adjustment up to 85%. Once the cells were trapped they were moved via a joystick system which enabled movement of the trap in three axis (x, y and z). The manipulation took place in an on-stage incubator and was captured via a CCD camera. Our study shows that via application of coating, selection of highly transmittable objective and facilitation of IR laser very large primary cells can be trapped and manipulated without the need of any handle beads and with no observable damage to survival. 30 µm diameter is the largest size the literatur holds to our knowledge This system can be used in cell culture for various experimental applications such as building micro-circuits of few cells for studies of network structure and function.

Disclosures: **B. Polat:** None. **S. Bay:** None. **G. Ozturk:** None.

Poster

827. Tracing and Imaging Methods

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 827.13/CC71

Topic: F.02. Animal Cognition and Behavior

Title: Long-term stability and flexibility in behaviorally relevant neural circuit dynamics

Authors: *A. K. DHAWALE[1], R. PODDAR[1], E. KOPELOWITZ[1], V. NORMAND[2], B. P. ÖLVECZKY[1];
[1]Harvard Univ., Cambridge, MA; [2]École Normale Supérieure, Paris, France

Abstract: Behavioral demands require that the brain generate highly stereotyped output when executing skilled actions while at the same time retaining the flexibility to switch between different tasks and learn new actions. How do neural circuits deal with these conflicting requirements for stability and flexibility over long timescales? Addressing this question requires tracking the activity of neuronal populations continuously over weeks and months in naturally behaving animals. Such experiments face significant technical challenges, including processing vast amounts of neural and behavioral data. We present an automated solution that overcomes these challenges, making it near effortless to continuously record and analyze neural activity in freely behaving rats over several months as the animals engage in normal daily activities and perform prescribed motor tasks in their home-cages. A key aspect of the system is a novel spike-sorting algorithm that allows for automatic identification and tracking of single units in terabyte-sized datasets even when units have non-stationary waveforms. We used our system to continuously record activity in large populations of single neurons in motor cortex, striatum, and thalamus. In conjunction with the neural recordings, high-resolution behavioral data was acquired using high-speed cameras and head-mounted 3-axis accelerometers. The behavioral data, in conjunction with local field potentials, were used to identify epochs of sleep, rest, grooming, feeding, and to track and quantify movement kinematics during the execution of a skilled motor sequence task. We found that firing rates and correlation structure in neuronal populations were stable across many days, even as they varied substantially across different behavioral states in a single day. Additionally, motor representations of skilled behaviors were found to be stable at the single unit level over month-long timescales. Our results demonstrate that neural circuits can maintain distinct task representations with remarkable long-term stability at the level of single neurons.

Disclosures: **A.K. Dhawale:** None. **R. Poddar:** None. **E. Kopelowitz:** None. **V. Normand:** None. **B.P. Ölveczky:** None.

Poster

827. Tracing and Imaging Methods

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Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: NIH Director's Pioneer award

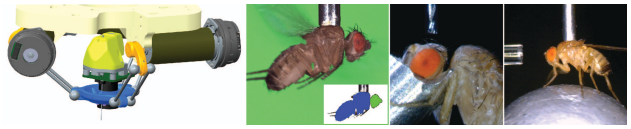
W.M. Keck Foundation

Stanford Bio-X program

Title: Dexterous robotic manipulation of alert adult fruit flies for high-content experimentation

Authors: ***J. SAVALL**[1,2], E. HO[1,4], C. HUANG[1], J. R. MAXEY[1], M. J. SCHNITZER[1,2,3]; [1]Clark Ctr., [2]Howard Hughes Med. Inst., [3]CNC Program, Stanford Univ., Stanford, CA; [4]Ctr. for Intelligent Signal and Imaging Res., Universiti Teknologi Petronas, Perak, Malaysia

Abstract: The fruit fly, *Drosophila* melanogaster, is widely used in research, but manual handling is often an experimental bottleneck. Here we present a dexterous high-speed robot that enables automated, high-content assessments of fly attributes and behavior. The robot can track and grab an alert fly's thorax, translate and rotate the picked fly, assess its phenotype and behavior, micro-dissect or release it, and rapidly interrogate multiple flies sequentially for diverse usages. By combining these elementary maneuvers, we used robotic handling to test flies' odor-evoked locomotor responses, sort flies by sex, dissect the cuticle to allow fluorescence imaging of neural activity, and quantitatively analyze body morphology through machine vision algorithms. Future, innovative usages of the robotic platform will likely exploit its capability for automated, quantitative measurement, the resulting statistical power that permits fine discriminations of fly morphology or active behavior, or the capacity to gently manipulate un-anesthetized flies in ways that humans cannot. Fast, automatic determination of fly sex provides the crucial ingredient for robotic establishment of fly matings, one of the most important in fly genetics. The robot can also perform many other analyses, handling tasks and surgical maneuvers for which humans lack the requisite dexterity or measurement precision. The capacity to catch and release individual flies will also allow novel time-lapse experiments involving automated, repeated examinations of individual flies' phenotypes across days or weeks. Overall, the robot has a tireless capacity for precise manipulations, is economical and readily scalable to multiple units, and thereby establishes a sophisticated technology platform for screening individual flies based on computerized appraisals of complex characteristics and behavioral responses.



Disclosures: **J. Savall:** None. **E. Ho:** None. **C. Huang:** None. **J.R. Maxey:** None. **M.J. Schnitzer:** None.

Poster

827. Tracing and Imaging Methods

Location: Hall A

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Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: NIH Grant (T32) 5T32NS073547-04

Title: How to build a powerful, flexible, and user-friendly light sheet microscope

Authors: *C. J. GREER[1], T. HOLY[2];
[1]Washington Univ. In St. Louis, Saint Louis, MO; [2]Washington Univ. in St. Louis, Saint Louis, MO

Abstract: Neuroscience laboratories are rapidly adopting light sheet microscopy as a tool to study neural circuits. The chief advantage of the technique is that thousands of neurons may be imaged at high speed with minimal photobleaching both *in vitro* and *in vivo*. Continuing improvements in fluorescent calcium indicators, voltage indicators, and optogenetic actuators are allowing neuroscientists to study physiology at an unprecedented scale. Yet light sheet microscopy is currently out-of-reach for many neuroscience laboratories: commercial microscopes are expensive, and building a microscope is challenging without optical expertise. In order make light microscopy more accessible, laboratories have begun to open-source the technology. I will contribute to this effort by presenting the design and assembly of a recently completed light sheet microscope to be shared by the neuroscience community in our institution. Our microscope uses the Objective Coupled Planar Illumination (OCPI) design. The system is capable of simultaneous two-color imaging and >5Hz scan rate through an entire larval zebrafish brain at cellular resolution. A second inverted brightfield microscope allows the user to more easily navigate the sample and to position electrodes for combining imaging with electrophysiology. Our design is also modular: users can easily switch between an axial scan mode and a horizontal scan mode that is more suitable for scanning along the cortical surface. Users are also free to remove the stage and replace it with custom equipment such as a spherical treadmill for mouse experiments. These features combine to result in a light sheet microscope that is at once powerful, flexible, and user-friendly.

Disclosures: C.J. Greer: None. **T. Holy:** None.

Poster

828. Technology Development: Magnetic Resonance Imaging and Positron Emission Tomography

Location: Hall A

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Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: Berzelii Technology Centre for Neurodiagnostics

Swedish Medical Research Council (Grant 9459)

Title: High-throughput screening and receptor binding reveal enzyme and GPCR targets as binding sites for a new PET tracer - D-deprenyl

Authors: A. A. LESNIAK[1], M. AARNIO[2], A. JONSSON[1], T. NORBERG[1], *F. J. NYBERG[1], T. GORDH[2];
[1]Uppsala Univ., Uppsala, Sweden; [2]Dept. of Surgical Sciences, Anaesthesiology and Intensive Care, Uppsala Univ. Hosp., Uppsala, Sweden

Abstract: Introduction and aim: D-deprenyl – an enantiomer of seligiline is a useful PET tracer for visualization of inflammatory processes. PET studies showed that peripheral D-deprenyl uptake is remarkably pronounced in patients suffering from chronic rheumatoid arthritis or musculoskeletal pain. High uptake points towards an existence of a yet non-characterized inflammation-specific binding site. Thus, the aim of our study was to identify the binding site for D-deprenyl via 1) commercial high-throughput screening towards 165 G-protein coupled receptors and 84 enzymes and 2) [H^3]D-deprenyl receptor binding analysis in rodent mitochondrial membrane and human inflamed synovial membrane preparations. **Methods**: D-deprenyl activity towards GPCR targets was assessed in CHO-K1 EDG1 β-arrestin EFC cell line with the PathHunter™ technique. Enzyme inhibition was assayed in the EnzymeProfiling™ screening panel. Binding studies with selective GPCR agonists and enzyme inhibitors at newly identified targets were performed in rat mitochondrial and human inflamed synovium preparations. **Results:** Our investigation revealed that D-deprenyl inhibits MAO-B, MAO-A and ACE activity by 99%, 55% and 70%, respectively. Binding studies confirmed a submicromolar [H^3]D-deprenyl competition with a selective MAO-B inhibitor seligiline, but not with the selective MAO-A inhibitor pirlindole mesylate. No evident hits among GPCR targets were identified. However, attention was drawn towards the histamine HRH1 and HRH3 receptors to which D-deprenyl showed a 20% and 42% antagonistic activity. **Discussion and conclusions:** MAO-B surfaced as a putative candidate target for D-deprenyl binding both in the mitochondrial and synovial membrane. Higher D-deprenyl uptake was documented in the CNS in activated astrocytes, non-secreting pituitary adenomas and at peripheral sites where MAO-B is overexpressed. Moreover, MAO-B expression is also present in the periphery in brown adipose tissue, fibroblasts and myocytes. Whereas, ACE inhibition by D-deprenyl could hamper down-regulation of transcription factors preventing ROS-mediated cartilage damage in animal models suggesting its role in inflammatory response.

Disclosures: **A.A. Lesniak:** None. **M. Aarnio:** None. **A. Jonsson:** None. **T. Norberg:** None. **F.J. Nyberg:** None. **T. Gordh:** None.

Poster

828. Technology Development: Magnetic Resonance Imaging and Positron Emission Tomography

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 828.02/CC75

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: NIH Grant R01NS091440

Wisconsin Alumni Research Foundation

ALS Association

Department of Defense

Title: Maximization of brain manganese uptake for PET/MRI in neurological applications

Authors: *C. M. LEWIS[1], S. A. GRAVES[1], R. HERNANDEZ[1], I. SMIT-OISTAD[2], R. J. NICKLES[1], M. E. MEYERAND[3], M. SUZUKI[2];
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Abstract: Manganese-enhanced MRI (MEMRI) has applications in anatomical and functional studies in rodents. The production of the PET isotope ^{52}Mn ($t_{1/2}$=5.6 days) has called interest to Mn-based PET/MRI and the possibility of ^{52}Mn PET in humans. Our group recently established proof of concept for tracking transplanted stem cells in the rat brain using Mn-based PET and MRI. Although the uptake and efflux of bulk doses of Mn^{2+} in the rodent brain are well established, the biodistribution of ^{52}Mn has yet to be thoroughly investigated. In this work, we study the uptake and retention of Mn^{2+} and ^{52}Mn in the rat brain with the aim of optimizing protocols for *in vivo* Mn-based PET/MRI. We first studied uptake of Mn^{2+} by observing R_1 relaxation rate (=1/T_1 relaxation time) with MRI. Female Sprague-Dawley rats (N=3 per group) were imaged prior to Mn delivery and over the course of two weeks following tail vein infusion of 30, 45, or 60 mg/kg $MnCl_2$. R_1 enhancement was observed at all time points and doses following $MnCl_2$ infusion. The greatest R_1 increase in the striatum of 84% was observed at the maximum dose 48 hours after contrast delivery. Despite high inter-subject variability in MRI contrast, a trend of increased R_1 enhancement at higher doses was observed. We next aimed to understand the dynamics of ^{52}Mn delivered both at tracer doses and supplemented with $MnCl_2$ at an MRI-appropriate dose. ^{52}Mn was diluted either in saline or in $MnCl_2$ solution then delivered by tail vein infusion at a dose of 2 mCi/kg. Brains were excised at days 1 and 2 post-contrast

(N=3 per group) and activity uptake was measured via gamma counting. A significant increase in brain activity of over 125% was observed in subjects delivered ^{52}Mn in saline (average 0.105%ID/g) compared to those delivered ^{52}Mn in $MnCl_2$ (average 0.044%ID/g). Three subjects underwent *in vivo* PET/CT over the course of 1 week beginning immediately following infusion of either no-carrier-added ^{52}Mn (N=2) or ^{52}Mn supplemented with bulk doses of $MnCl_2$ (N=1). It was found that the maximum brain-averaged uptake of 0.22%ID/g was reached by infusing no-carrier-added ^{52}Mn in saline and imaging the subject approximately 4 hours following infusion. These data lay the groundwork for Mn-based PET/MRI imaging protocols in rodent neurological applications. We observed reduced ^{52}Mn uptake in the brain when supplemented with bulk $MnCl_2$, which is an important consideration for designing *in vivo* PET/MRI imaging protocols. Importantly, *in vivo* PET imaging revealed low but detectable brain uptake of ^{52}Mn.

Disclosures: C.M. Lewis: None. **S.A. Graves:** None. **R. Hernandez:** None. **I. Smit-Oistad:** None. **R.J. Nickles:** None. **M.E. Meyerand:** None. **M. Suzuki:** None.

Poster

828. Technology Development: Magnetic Resonance Imaging and Positron Emission Tomography

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 828.03/CC76

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: NIH Grant R21AG045637

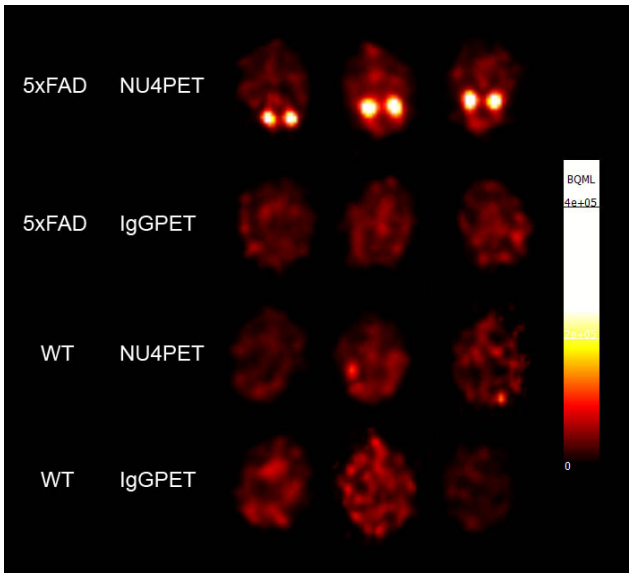
NUCATS Grant FY2104-2015

Title: Development of a PET tracer that targets amyloid β oligomers (AβOs)

Authors: *K. L. VIOLA[1], T.-T. CHANG[3,4], E. N. CLINE[1], E. CHUNG[5], M. DYKSTRA[3,4], B. MERRIFIELD[3,4], A. PECK[3,4], A. L. QIN[1], C. VALDEZ[1], H. J. WEISS[1], L. R. ZIESKE[6], W. L. KLEIN[1,2];
[1]Neurobio., Northwestern Univ., Evanston, IL; [2]Neurol., Northwestern Univ., Chicago, IL; [3]Small Animal Imaging Facility, [4]Lab. of Translational Imaging, Van Andel Res. Inst., Grand Rapids, MI; [5]Illinois Math & Sci. Acad., Aurora, IL; [6]Singulex, Inc., Alameda, CA

Abstract: The introduction of PET probes for amyloid plaques has shown that molecular imaging can be an important tool for Alzheimer's drug development. It is known, however, that amyloid plaques are not present in the earliest stages of the disease, and they no longer appear to

be the instigating cause of nerve cell damage. Probes for alternative markers, especially for the earliest stages of AD, are needed for effective disease intervention and management. Studies over the last 15 years indicate that pathogenic amyloid beta oligomers (AβOs) may be a more appropriate biomarker. AβOs cause the synapse failure regarded as responsible for AD memory loss, can be linked to major aspects of AD pathology, and appear early in the disease (Viola & Klein, 2015, Acta Neuropathol, 129(2):183-206). Antibody localization has been found to show a clear separation of AβOs from ThioS-positive plaques. These AβO-antibodies, when coupled to a magnetic nanostructure (NU4MNS), have been used experimentally to obtain an AD-relevant MRI signal (Viola et al, 2015, Nat Nanotechnol, 10(1):91-8). Because PET is more sensitive, an analogous antibody-based PET probe would be expected to be useful for earlier detection. Initial experiments have used the 5xFAD transgenic mice. AβOs in these animals begin to accumulate before the onset of memory dysfunction, as shown by histochemistry and an ultra-sensitive Erenna®-based assay (research use only). Initial tests of our antibody-based PET probe, NU4PET, were designed to determine if it can cross the blood-brain barrier and provide a disease specific signal. Virtually no signal was found in controls (rows 2-4: IgGPET in 5XFAD mice; NU4PET & IgGPET in wild type littermates). However, as predicted, in 5XFAD mice injected with NU4PET, brains were found to exhibit robust PET signals (top row).



Disclosures: **K.L. Viola:** None. **T. Chang:** None. **E.N. Cline:** None. **E. Chung:** None. **M. Dykstra:** None. **B. Merrifield:** None. **A. Peck:** None. **A.L. Qin:** None. **C. Valdez:** None. **H.J. Weiss:** None. **L.R. Zieske:** None. **W.L. Klein:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Acumen Pharmaceuticals, Inc..

Poster

828. Technology Development: Magnetic Resonance Imaging and Positron Emission Tomography

Location: Hall A

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Program#/Poster#: 828.04/CC77

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: NIH grant R01 DA028299

NIH grant R01 NS076462

Edmond & Lili Safra Center (ELSC) Postdoctoral Fellowship

European Molecular Biology Organization (EMBO) Postdoctoral Fellowship

Title: *In vivo* magnetic resonance imaging of neurotransmitter reuptake

Authors: *A. HAI, L. X. CAI, T. LEE, V. S. LELYVELD, A. P. JASANOFF;
Biol. Engin., MIT, Cambridge, MA

Abstract: Molecular imaging of dynamic processes in the brain is highly challenging and currently relies on modalities such as positron emission tomography (PET) which offers high specificity but relatively low temporal and spatial resolution and requires the use of radio-labeled ligands. We present the use of a novel protein-based serotonin binding MRI sensor for the detection of serotonin reuptake kinetics *in vivo*. Brain injection of the sensor with and without serotonin into the striatum of anesthetized rats, demonstrates a clear difference in MRI signal kinetics as a result of unbinding of serotonin from the sensor. Systemic injection of the serotonin transporter inhibitor (SSRI) fluoxetine blocks reuptake and reverses the MRI signal increase. Spatial maps of serotonin reuptake in conjunction with kinetic modeling allow for the first time to explore neurotransmitter transport and inhibition by anti-depressant drugs using MRI.

Disclosures: A. Hai: None. **L.X. Cai:** None. **T. Lee:** None. **V.S. Lelyveld:** None. **A.P. Jasanoff:** None.

Poster

828. Technology Development: Magnetic Resonance Imaging and Positron Emission Tomography

Location: Hall A

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Program#/Poster#: 828.05/CC78

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: GA CR P304/12/1370

MEYS LO1309

Title: Cobalt zinc ferrite nanoparticles - a suitable tool for magnetic cell labeling

Authors: *P. JENDELOVA[1], B. NOVOTNA[1], K. TURNOVCOVA[1], M. VEVERKA[2], P. ZVATORA[2], V. HERYNEK[3], Y. BAGRYANTSEVA[1], E. SYKOVA[1];
[1]Inst. of Exptl. Medicine, ASCR, Prague 4, Czech Republic; [2]Inst. of Physics, ASCR,, Prague, Czech Republic; [3]Inst. for Clin. and Exptl. Med., Prague, Czech Republic

Abstract: Objectives To monitor the fate of transplanted cells within an organism, several non-invasive techniques have been introduced, including magnetic resonance imaging (MRI) of cells labeled with a contrast agent prior to grafting. Our previous study demonstrated a severe oxidative injury to lipids, proteins and the DNA of human bone marrow mesenchymal stem cells as a result of their labeling with superparamagnetic iron oxide nanoparticles. In searching for new contrast agents and magnetic cell labels, we prepared and tested a contrast agent based not only on Fe, but also on Co and Zn [cobalt zinc ferrite Co0.5Zn0.5Fe2O4+γ (CZF)] with a core encapsulated by amorphous silica. Methods Rat mesenchymal stem cells (MSCs) were labeled for 48 hour with 3 different concentrations of CZF particles, containing 7.5ug CZF/ml, 15ug CZF/ml and 75ug CZF/ml. Cell viability was assessed by trypan blue exclusion, and PI/Annexin V labeling was used to estimate the percentages of viable and dying cells. Cell proliferation was measured using a xCELLigence Real Time Cell Analyzer. To evaluate the genotoxicity of CZF nanoparticles, MSCs were labeled with all three concentrations of nanoparticles and then assessed for oxidative damage to their DNA (comet assay). MSCs labeled with CZF nanoparticles were differentiated into osteo-, chondro- and adipogenic phenotypes in appropriate differentiation media. Relaxivity was measured by a 20MHz Bruker Minispec relaxometer for the two lower concentrations only. The amount of Fe, Co and Zn in the cells was analyzed by the ICP/MS method. Results The two lower concentrations did not affect cell viability, while the highest concentration slowed down cell proliferation. Only the highest CZF dose increased DNA strand breaks (5.5x) and oxidative DNA damage (17x) above the control levels, while no obvious genotoxic effect was noticed in cells labeled with the two lower CZF doses. Differentiation into adipo-, osteo- and chondrogenic phenotypes was not affected by cell labeling at all. The relaxation rate of a cell suspension labeled at a concentration of 7.5ug CZF/ml was 0.85 s-1/million cells/ml, while the rate of cells labeled at a concentration of 15ug CZF/ml reached 1.55 s-1/million cells/ml and 1000 cells were visible as hypointense signal in rat brain. The average amount of magnetic ions inside one cell was 2.77 pg Co, 10.19 pg Fe and 4.28 pg Zn for a CZF concentration of 7.5ug CZF/ml and 6.35 pg Co, 27.97 pg Fe and 6.01pg Zn for a concentration of 15ugCZF/ml. Conclusions Concerning their safety for biomedical applications and their

suitability for MR tracking, CZF particles represent a very promising contrast agent suitable for cell labeling.

Disclosures: **P. Jendelova:** None. **B. Novotna:** None. **K. Turnovcova:** None. **M. Veverka:** None. **P. Zvatora:** None. **V. Herynek:** None. **Y. Bagryantseva:** None. **E. Sykova:** None.

Poster

828. Technology Development: Magnetic Resonance Imaging and Positron Emission Tomography

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 828.06/DD1

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: Department of Defense grant

J. Crayton Pruitt Family Endowment

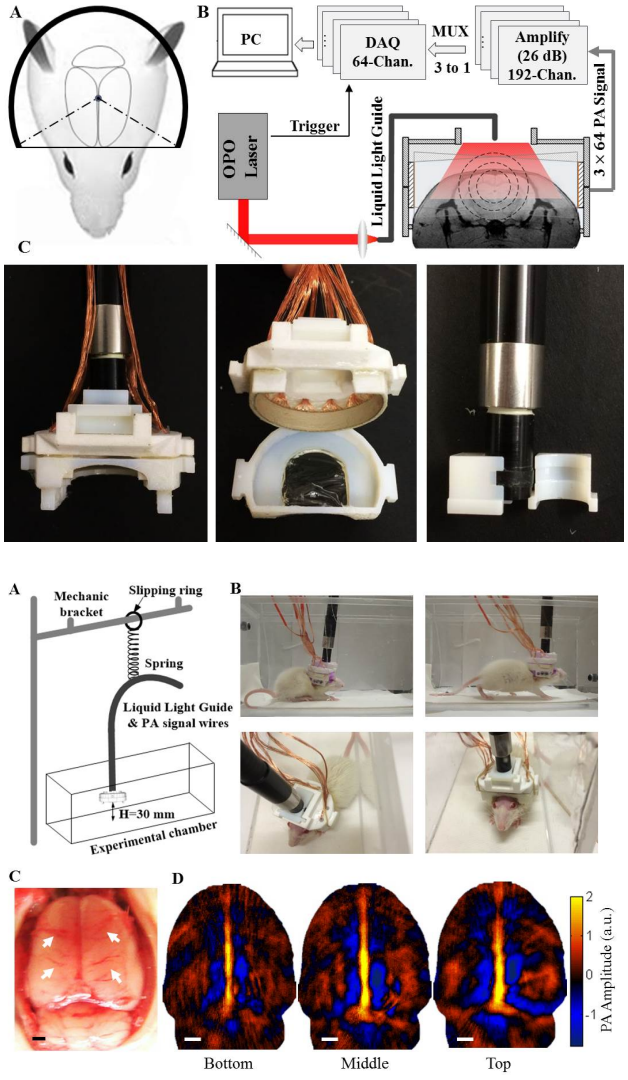
B.J and Eve Wilder Center of Excellence for Epilepsy Research

Title: 4-D wearable photoacoustic tomography for non-invasive imaging of cerebral hemodynamics in behaving rats

Authors: *J. TANG[1], J. ZHOU[2], P. CARNEY[2], H. JIANG[1];
[1]Biomed. Engin., [2]Dept. of Pediatrics, Univ. of Florida, Gainesville, FL

Abstract: We present a non-invasive wearable photoacoustic tomography (wPAT) system for 4-D imaging of cerebral hemodynamics in behaving rats. The 2nd generation wPAT system (2nd-G-wPAT) has 3 layers of transducer arrays, and has a size of 20 mm in height and 44 mm in diameter, and a weight of ~12 g (excluding cabling). It solved the vision occlusion problem that encountered in the previous design, and can obtain 3 layers' whole brain cross-sectional images within 0.3 s with an X-Y plane lateral resolution of 228 μm. The 2nd-G-wPAT's imaging ability has been demonstrated through a series of rat experiments, including hyperoxia functional imaging, PTZ-induced generalized seizure, 4-AP induced focused seizure, decision-making when challenged with cold/warm water, and emotional test by adding companion during experiment. The cerebral hemodynamic changes were successfully captured by the 2nd-G-wPAT in all testing experiments. Our studies suggest that this 4-D wAPT has the potential to be used in a wide range of behaving animal studies involving cerebral oxygen saturation monitoring, brain metabolism rate detection, visual learning/rewarding, behavior and cognition study, emotions,

stress, and brain disorders. It, therefore, may become a powerful tool for the neuroscience community.



Disclosures: **J. Tang:** None. **J. Zhou:** None. **P. Carney:** None. **H. Jiang:** None.

Poster

828. Technology Development: Magnetic Resonance Imaging and Positron Emission Tomography

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 828.07/DD2

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: BBSRC ISPG

Title: Quantitative tissue analysis with infrared imaging technology

Authors: *S. EATON[1,2], E. CUMYN[2,3], D. KING[2], R. KLINE[2], S. CARPANINI[2], J. DE POZO[3], R. BARRON[2], T. M. WISHART[2,4];
[1]Neurobio., Univ. of Edinburgh, Penicuik, United Kingdom; [2]Roslin Institute, Univ. of Edinburgh, Penicuik, United Kingdom; [3]Royal (Dick) Sch. of Vet. Studies, Penicuik, United Kingdom; [4]Euan MacDonald Ctr. for Motor Neurone Dis. Res., Edinburgh, United Kingdom

Abstract: Immunohistochemistry (IHC) is a key technique in the neurobiologists tool box used to identify specific antigens in order to characterise protein distribution and relative abundance within histological samples. Capture of images can be time consuming and their analysis can prove inherently difficult to quantify. Typically, quantification requires sophisticated software or complex normalisation parameters. Conventional fluorophores are not necessarily linear in their expression profiles and non-fluorescent methodologies, including diaminobenzine (DAB) label deposition, are not truly directly proportional to the expression of the targeted protein therefore IHC results are considered semi-quantitative. Recent advances in imaging using infrared (IR) "tags", with an appropriate scanner, provides an alternative system where the linear nature of the IR fluorophore emittance enables realistic Quantitative Fluorescence Immunohistochemistry (QFIHC) with little background. Furthermore, such a system allows entire tissue sections to be scanned yielding accurate area and protein abundance measurements from swiftly acquired tissue images. Here, we demonstrate that image capture and analysis using IR scanning technology produces comparable area based quantification to those obtained from a Hamamatsu Nanozoomer-XR slide scanner combined with ImageJ analysis. We demonstrate the scanners capacity for dual target visualisation within tissue sections. Additionally, we compare the distribution of two well-characterised proteins labelled using traditional biotin/streptavidin complex in conjunction with DAB or modern IR tagged secondary antibodies and conclude that IR based IHC produces images of comparable quality to that seen with DAB-labelled sections captured with light microscopy at X20 magnification regardless of upstream tissue processing methodology. Furthermore, by comparison with quantitative fluorescent western blotting (QFWB) data from microdissected brain regions we demonstrate that IR based relative protein abundance QFIHC measurements are an accurate reflection of tissue sample abundance. Thus, we suggest that IR based QFIHC employing an Odyssey scanner from LI-COR provides an alternative method of rapid low resolution imaging of whole brain sections for the production of reliable and accurate quantitative data.

Disclosures: **S. Eaton:** None. **E. Cumyn:** None. **D. King:** None. **R. Kline:** None. **S. Carpanini:** None. **J. De Pozo:** None. **R. Barron:** None. **T.M. Wishart:** None.

Poster

828. Technology Development: Magnetic Resonance Imaging and Positron Emission Tomography

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 828.08/DD3

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: CIHR

NIH

Title: Atlas of forgotten dimensions: creating a metallome for epilepsy and beyond

Authors: *E. L. OHAYON[1,2], A. LAM[1,2];
[1]The Green Neurosci. Lab., Neurolinx Res. Inst., San Diego, CA; [2]Univ. of Toronto Epilepsy Res. Program, Toronto, ON, Canada

Abstract: Current efforts at uncovering "omes", in rough order of scale, have focused on the brain genome, proteome and, most recently, the connectome. However, a more fundamental aspect of the brain -- the elemental makeup at the atomic level -- is often overlooked. In this study we use synchrotron-based x-ray fluorescence imaging (SXRF) and other complementary techniques to map the spatial distribution of brain metals at resolutions of up to 1 micron with even higher resolutions on the horizon. Our dataset thus begins at 4D, reflecting the three spatial dimensions with the co-localization of metals constituting a fourth. We also implicitly add a temporal dimension by studying metals at different stages of development afforded through iPSCs, post-surgical and postmortem tissue studies. Samples include epilepsy tissue (post-surgical) as well as typical and Williams Syndrome (iPSCs and postmortem). We describe how the data is being prepared for an online open metal atlas. We also illustrate how the availability of this metallome could be essential for identifying new (i) biomarkers (ii) mechanisms and (iii) clinical therapies. Finally, we describe how the data may even help connect to an "ome" at the very other end of spatial scales, namely the "exposome" and consider how it may aid in environmental exposure assessment in neural tissue. (Atlas hosted at: http://greenneuro.org/atlas/).

Disclosures: **E.L. Ohayon:** None. **A. Lam:** None.

Poster

828. Technology Development: Magnetic Resonance Imaging and Positron Emission Tomography

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 828.09/DD4

Topic: G.03. Staining, Tracing, and Imaging Techniques

Title: A small-molecule approach to the detection of aromatase activity in gonadal and non-gonadal tissues

Authors: *D. S. MCCARTHY[1], L. REMAGE-HEALEY[2,3], J. J. CHAMBERS[3,1];
[1]Dept. of Chem., [2]Dept. of Psycological and Brain Sci., [3]Dept. of Neurosci. and Behavior, Univ. of Massachusetts, Amherst, MA

Abstract: The goal of our current research is to develop a small molecule that can report on the activity of aromatase in tissue lysate and intact tissue including neural structures. To accomplish this, we have designed a novel, non-steroidal fluorogenic molecule that behaves as a substrate for aromatase, a cytochrome P450, family 19, subfamily A, polypeptide. Inspired by the structure of the native substrate, testosterone, our coumarin based small molecule is designed to undergo the same stepwise aromatization organic mechanism, thus converting an alpha, beta-unsaturated ketone into an aromatic ring that is in conjugation with the coumarin fluorophore. The effect of aromatization is to extend the pi-electron system of the fluorophore and to red-shift the emission wavelength of the coumarin. Analysis with tandem mass spectrometry of samples from *in vitro* experiments utilizing our substrate and gonadal tissue (zebra finch ovary) or sham treatments has indicated that we are able to convert the substrate into the aromatized product when active aromatase is present. These data, along with synthetic strategies, future designs, and fluorescence data will be presented and discussed.

Disclosures: D.S. McCarthy: None. **L. Remage-Healey:** None. **J.J. Chambers:** None.

Poster

828. Technology Development: Magnetic Resonance Imaging and Positron Emission Tomography

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 828.10/DD5

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: HHMI Funding

Title: Visualizing neurite ultrastructure by electron cryotomography of cultured neurons

Authors: *M. T. SWULIUS, S. WEAVER, G. JENSEN;
Biol., Caltech, Pasadena, CA

Abstract: Electron Cryotomography (ECT) provides 3D molecular-resolution images of hydrated cells, allowing unprecedented preservation of cellular structure and macromolecular complexes in the cytoplasm. Here we use ECT to study the neurite morphology, organelles, cytoskeleton and cytoplasmic environment of axons and dendrites in cultured rat hippocampal neurons. We examine the *in vivo* structure of microtubules, neurofilaments and actin networks, as well as a cortical network of fine filamentous proteins situated near the membrane of dendrites. Subtomogram averaging is used to identify TriC chaperone complexes in the cytoplasm, and the formation of TriC clusters and their spatial relationship to polysomes in the cytoplasm is examined. The future of neuronal imaging by ECT and its potential to further investigate the dynamic molecular architecture of neurons will be discussed.

Disclosures: **M.T. Swulius:** None. **S. Weaver:** None. **G. Jensen:** None.

Poster

828. Technology Development: Magnetic Resonance Imaging and Positron Emission Tomography

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 828.11/DD6

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: CIHR

CHRP

Title: A novel miniature multimodal imaging system to simultaneously monitor and measure brain ion fluxes, blood flow and oxygenation during seizure-like events in non-anesthetized freely behaving rats

Authors: *M. A. JEFFREY[1], D. RINGUETTE[2], I. SIGAL[2], R. GAD[2], P. CARLEN[1], O. LEVI[2];

[1]Fundamental Neurobio., Toronto Western Res. Inst., Toronto, ON, Canada; [2]Dept. of Electrical and Computer Engin., Inst. of Biomaterials and Biomed. Engin., Toronto, ON, Canada

Abstract: The spatiotemporal relationships between ion flux, blood oxygenation and blood flow are not well understood with respect to seieizures/ epileptogenesis. Robust quantitative measures of excitability, ion flux and vascular dynamics have not been possible due to the following technical limitations: 1) 1) Spatial resolution of local field potential measures is limited to the tips of electrodes;; 2) 2) When measuring ionic activity with fluorescent dyes, 3) Laser Doppler imaging systems are relatively large, and their imaging of blood flow is limited by low spatial resolution; 3) 4) Anesthetics alter brain excitability, inflammation, and blood flow. To address these challenges we designed a novel multimodal optical imaging system suitable for chronic studies. The system uses a fast camera and verticalcavity laserVCSEL sources, imaging through a cranial window with a large FOV. The system measures blood flow with using LCSI, oxygenation with IOSI, and ion flux using fluorescence. Anesthetized and ratsRats are injected with PTZgiven acute injections of low doses of pentylenetetrazol to induce a spectrum of seizure-like events. Measures are made in the presence and absence of anticonvulsant and gap-junction blocking drugs with differing effects on calcium and potassium comductance. A single bipolar stainless steel electrode in the sensorimotor cortex records the concomitant reference EEG signal. Quantitative measures from our recordings used to demonstrate the efficacy of our imaging system in assessing the simultaneous spatiotemporal dynamics of ion flux and hemodynamics. Correlation of dynamic calcium and potassium flux with blood flow/oxygenation is particularly of interest, since these fluxes are altered during epileptogenesis and ictogenesis. This imaging system allows us , for the first time, to study relationships and interactions between seizures-like events, blood flow/w and oxygenation, and ion flux with very high spatiotemporal fidelity. It could,, have major implications in the diagnosis and treatment of neurological disorders.

Disclosures: **M.A. Jeffrey:** None. **D. Ringuette:** None. **I. Sigal:** None. **R. Gad:** None. **P. Carlen:** None. **O. Levi:** None.

Poster

828. Technology Development: Magnetic Resonance Imaging and Positron Emission Tomography

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 828.12/DD7

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: CIHR

Title: Do trace metals levels differ in cases of refractory epilepsy? Insights from synchrotron x-ray fluorescence studies of human resected tissue

Authors: *A. LAM[1,2], S. WEBB[3], B. D. KOCAR[3], T. A. VALIANTE[4], P. L. CARLEN[4], E. L. OHAYON[1,2];
[1]Green Neurosci. Lab., Neurolinx Res. Inst., San Diego, CA; [2]Univ. of Toronto Epilepsy Res. Program, Univ. of Toronto, Toronto, ON, Canada; [3]Stanford Synchrotron Radiation Lightsource, Menlo Park, CA; [4]Toronto Western Res. Inst., Toronto, ON, Canada

Abstract: Changes in biological processes dependent on trace metals (e.g., iron, zinc, copper, chromium, selenium, etc.) have been linked to epilepsy. The extent to which the metals themselves play a role is unclear due to the limitations in current techniques that result in the loss of structural information in order to detect metals levels in samples. We have previously described our advancements in synchrotron x-ray fluorescence (SXRF) imaging of human brain tissue which enables researchers to attain spatial information (e.g., in terms of colocalized distribution of metals), as well as the quantification of metals within user-defined areas. We have shown that SXRF is sufficiently sensitive to detect trace metal concentrations in cell cultures, postmortem and surgically resected tissue. In addition, SXRF enables us to co-register our metal maps to known substructures in the hippocampus and cortex. Here we examine differences between resected brain tissue recovered from minimally invasive epilepsy surgery to treat individuals with medically refractory epilepsy. Differences were observed between cortical and hippocampal tissue in copper and zinc levels in some, but not all individuals. These results suggest a potential subgroup of medically intractable epilepsies involving copper.

Disclosures: A. Lam: None. **S. Webb:** None. **B.D. Kocar:** None. **T.A. Valiante:** None. **P.L. Carlen:** None. **E.L. Ohayon:** None.

Poster

829. Data Analysis: Human and Networks

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 829.01/DD8

Topic: G.07. Data Analysis and Statistics

Support: Dean's Tuition Fellowship

CMU Startup

Title: Is the direction of Granger causal influence the same as the direction of information flow?

Authors: *P. VENKATESH, P. GROVER;
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Abstract: Granger causality and, more recently, Directed Information, have shown potential as measures of directed ``causal influence". Of late, many works have interpreted this direction of causal influence as being the direction of ``information flow" through neural pathways. We ask whether this interpretation is always correct by testing it on simple feedback models from communications theory. What, precisely, do we mean by information flow, and how is it different from causal influence? Causal influence, here, is simply a result of measures such as Granger causality. We think of information flow, on the other hand, in the more abstract sense of different parts of the brain sending messages to each other. If we consider just two parts of the brain as comprising a communication system, then it is of neuroscientific importance to understand which region is sending messages to the other, i.e., where did the information arrive first, and where did it thereafter go? Today, Granger causality and directed information are commonly used to infer this direction of information flow. We claim, using results motivated by information theory, that Granger causality *cannot* always correctly identify the direction of information flow (the direction in which the message is being passed). Our counterexamples are based on simple feedback systems where a transmitter communicates to a receiver using a well-known information theoretic strategy pioneered by Schalkwijk and Kailath in 1966. In these examples, the ``ground truth" for the direction of information flow is known by construction: from the transmitter to the receiver. We consider the case of communicating both a non-time-varying, as well as a time-varying message, using auto-regressive models (that are widely used to represent Local Field Potentials) for the latter. We show that for reasonable values of model parameters, even for this two-node problem, the direction of information flow can be opposite to the direction indicated by Granger causality and Directed Information. We believe that this interpretation only becomes more questionable for larger networks. We conclude that one needs to exercise care in interpreting the direction of Granger causal influence as the direction of information flow.

Disclosures: **P. Venkatesh:** A. Employment/Salary (full or part-time):; Carnegie Mellon University, Department of Electrical and Computer Engineering. Other; Dean's Tuition Fellowship. **P. Grover:** A. Employment/Salary (full or part-time):; Carnegie Mellon University, Department of Electrical and Computer Engineering. Other; CMU startup.

Poster

829. Data Analysis: Human and Networks

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 829.02/DD9

Topic: G.07. Data Analysis and Statistics

Support: NIH grant R01MH102840

Title: Calibration of extracellular spike models of monosynaptic dynamics using intracellular recordings

Authors: *J. PLATKIEWICZ[1], D. F. ENGLISH[2], E. STARK[2,3,4], P. P. QUILICHINI[5], G. BUZSÁKI[2], A. AMARASINGHAM[1];
[1]Dept. of Mathematics, The City Col. of New York, The City Univ. of New York, New York, NY; [2]Neurosci. institute, Sch. of Med., New York Univ., New York, NY; [3]Dept. of Physiol. and Pharmacology, Sackler Fac. of Med., [4]Sagol Sch. of Neurosci., Tel Aviv Univ., Tel Aviv, Israel; [5]Inst. de Neurosciences des Systemes, Aix Marseille Univ., Marseille, France

Abstract: Synaptic connectivity has been identified from large datasets of extracellular spikes in the freely moving rat, using cross-correlation-type statistics (Barthó et al, 2004; Fujisawa et al, 2008). There are, however, numerous concerns regarding the analysis: spikes are an impoverished representation of a cell's membrane activity; cell detection and identification result from numerous indirect inferences; detecting synaptic connectivity from a cross-correlogram observation is an ill-posed problem. Motivated by these issues, we aimed at testing the spike train model used in (Fujisawa et al, 2008) on more direct measurements of cellular firing behavior. For that, we examined paired intracellular-extracellular recordings in anesthetized rats (Quilichini et al, 2010), and freely moving mice (English et al, 2014). First, we developed predictions about membrane potential fluctuations based on the spike train model. For this purpose, we used simple biophysical spiking models, whose parameters were adjusted to the intracellular data, and simple synapse models. Second, we tested these predictions on the paired intracellular-extracellular recordings. This work provides an attempt to reconcile spike train and biophysical models in the same framework, with the purpose of detecting and identifying more systematically synaptic connectivity under *in vivo* conditions. In particular, we highlight how the parameters extracted from extracellular data relate to biophysical parameters, typically estimated from intracellular data.

Disclosures: J. Platkiewicz: None. **D.F. English:** None. **E. Stark:** None. **P.P. Quilichini:** None. **G. Buzsáki:** None. **A. Amarasingham:** None.

Poster

829. Data Analysis: Human and Networks

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NIMH Grant MH081928

NIMH Grant MH082004

NIMH Grant MH082022

NIMH Grant MH081984

NIMH Grant MH066160

Title: Reliability of multi-site functional connectivity

Authors: *S. M. NOBLE[1], D. SCHEINOST[2], R. T. CONSTABLE[3], T. D. CANNON[4];
[1]Interdepartmental Neurosci. Program, [2]Diagnos. Radiology, [3]Diagnos. Radiology, Neurosurg., [4]Psychology, Yale Univ., New Haven, CT

Abstract: Functional magnetic resonance imaging (fMRI) connectivity maps are often combined or compared across multiple fMRI scanning sites to improve analytical power, but the validity of pooling multi-site data given scanner-related variability remains under-investigated. The reliability of connectivity across sites was assessed using a sample from the North American Prodrome Longitudinal Study (NAPLS) comprising healthy subjects (n = 8 subjects) who were each scanned at every site in the NAPLS consortium (n = 8 sites) on two consecutive days. The brain was parcellated into functional subunits using a 278-node functional connectivity atlas. Two measures of connectivity were investigated: whole brain voxel-wise connectivity, as measured by the intrinsic connectivity distribution (ICD), and standard seed connectivity relative to network hubs (i.e., PCC, motor cortex, thalamus). Mean reliability of ICD was found to be excellent across sites and days (mean generalizability ICC = 0.7809). Mean reliability of connectivity between network hubs and the whole brain was found to be fair (mean ICC = 0.55). Seed connectivity maps were further subdivided into subnetworks evidencing excellent reliability (ICC > 0.74) and networks evidencing poor reliability (ICC < 0.4). Subnetworks evidencing excellent reliability contained edges highly consistent with previously classified networks (e.g., the PCC - mPFC edge in the default mode network). Subnetworks evidencing poor reliability often contained edges outside of recognized networks and distributed throughout the brain (e.g., a PCC - left putamen edge). These results suggest that future multi-site connectivity studies involving edges outside of previously classified networks warrant further

investigation to address issues of poor reliability; these issues may be attributable to some combination of intrinsic factors, e.g., weak connectivity, and multi-site effects.

Disclosures: **S.M. Noble:** None. **D. Scheinost:** None. **R.T. Constable:** None. **T.D. Cannon:** None.

Poster

829. Data Analysis: Human and Networks

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Program#/Poster#: 829.04/DD11

Topic: G.07. Data Analysis and Statistics

Support: NRF-2011-0027921

Samsung Electronics Co. Ltd.

Title: A novel re-referencing method for ERP based brain-computer interfaces

Authors: ***M.-K. KIM**;
UNIST, Ulsan, Korea, Republic of

Abstract: Scalp electroencephalography (EEG) is one of the brain signal measurements, which is widely used in the development of brain-computer interfaces (BCIs) not only for patients with tetraplegia but also as applications for the able-bodied. Especially, an event-related potential (ERP) based BCI is a technology known to yield high accuracy and information transfer rate. Still, some users cannot achieve reliable BCI performance due to inability to generate fine ERP waveforms. The ERPs contain time-locked features elicited by an external stimulus, and factors that have direct negative influences such as artifacts can be overcome by either multi-trial averaging or adopting various de-noising methods. However, there are reports of another factor that has an indirect influence on the generation of ERPs: phase-resetting from the thalamocortical oscillations (TOs) known to be associated with the EEG pacemaker. The influences of the TOs are task dependent. Particularly, changes of alpha activity in the TOs are affected by visual stimuli and observed in the occipital area. Thus, ERPs measured during a visual task may be seen as a mixture of activities associated with visual information from occipital areas as well as various cognitive functions from many other areas. Under such a hypothesis, we suggest a new re-referencing method that enables detection of clearer ERPs by subtracting TO-related visual components from EEG measurements in each channel location. The TO-related visual components were estimated using the first principal component of the

multiple occipital channels (O1, O2, and Oz). For evaluation, we conducted an experiment in twenty healthy volunteers who performed a visual oddball task with flickers designed to simulate an online TV channel selection scenario using a P300-based BCI. Online performance was compared among four methods: no re-referencing, Laplacian filter, common averaging, and the proposed re-referencing method. The proposed method allowed acquisition of more pronounced ERP waveforms and also yielded superior online BCI performance than other methods: the overall accuracy was 75 ±14.7% for the proposed method, 55±18.1% for the Laplacian filter, 52±13.9% for the common averaging and 51±14.7% without re-referencing, respectively. The result suggests that the proposed method to re-reference EEG signal could help obtain improved ERPs in visual tasks. While this study limited its scope to task-dependent re-referencing for ERP based BCIs, our future focus will be the development of a more generalizable task-independent re-referencing method.

Disclosures: M. Kim: None.

Poster

829. Data Analysis: Human and Networks

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 829.05/DD12

Topic: G.07. Data Analysis and Statistics

Support: Contract with the National Institute of Information and Communications Technology No.173

Title: Experimental validation of hierarchical Bayesian diffuse optical tomography algorithm for human brain function studies

Authors: *O. YAMASHITA[1], T. SHIMOKAWA[1], R. AISU[1,2], T. AMITA[3], Y. INOUE[3], M. SATO[1];
[1]ATR, Kyoto, Japan; [2]Nara Inst. of Sci. and Technol., Nara, Japan; [3]Shimadzu Corp., Kyoto, Japan

Abstract: The multi-channel continuous wave near infrared spectroscopy (NIRS) is used to investigate human brain functions. However lack of ability to specify activity location on brain anatomy is one of big issues to interpret activity spatial patterns. Diffuse optical tomography (DOT) is an emerging technology for improving the spatial resolution and spatial specificity of conventional multi-channel near infrared spectroscopy by means of high density measurement and image reconstruction algorithm. Although any DOT algorithm has the ability to reconstruct

scalp and cortical hemodynamics changes in their respective layers, which are the two main contributors of NIRS measurement, no DOT algorithm has been proposed to achieve accurate separation of these changes. Previously we have proposed a hierarchical Bayesian DOT algorithm in which the distinct nature of scalp and cortical hemodynamics changes is modeled and verified its performance with phantom experiment, computer simulation and human experimental data of one subject (Shimokawa et al. 2013, Yamashita et al. 2014). Here we extend the previous human case study to multi-subject and multi-task study to show validity of the algorithm to wider population and task conditions. We measured brain activities during right hand movement, right index finger movement and no right hand movement from 12 subjects using high-density NIRS and fMRI in two different sessions. DOT reconstruction performance is quantified with localization error (LE), area under curves (AUC) and spatial pattern similarity (SS) using fMRI activity maps as ground-truth. Median LE, AUC and SS for hand and finger conditions were about 6 and 8 mm, 0.86 and 0.84, 0.62 and 0.42, respectively. AUC and SS of our algorithm were significantly better than those of the standard DOT algorithm (depth-compensation minimum norm algorithm). In no-movement condition, our method successfully reconstructed no activity while the standard method showed some spurious activities. In conclusion, this study showed feasibility of our algorithm for wider subject population and wider task conditions and superiority to the standard DOT algorithm.

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Poster

829. Data Analysis: Human and Networks

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Topic: G.07. Data Analysis and Statistics

Support: DoD Contract N66001-14-2-4032

Title: Performance of an adaptive interictal spike detection algorithm

Authors: ***S. MEISENHELTER**[1], P. C. HORAK[2], A. CONNOLLY[2], B. JOBST[2];
[1]Neurol., Geisel Sch. of Med. At Dartmouth, Lebanon, NH; [2]Geisel Sch. of Med. at Dartmouth, Hanover, NH

Abstract: The identification of epileptiform activity and recording artifacts is crucial for the analysis of electrocorticography (ECoG) data. For the study of human brain activity, for clinical

diagnostics, and for the study of epilepsy, it is desirable to detect and classify spikes and other epilepsy related signals automatically. For many scientific studies, the removal of these waveforms is an indispensable pre-processing step. In humans, effective algorithms for the automatic detection and classification of epileptiform activity remain elusive partially due to the difficulty in defining the characteristics of an interictal spike. The morphology of interictal spikes varies considerably between patients. However, epileptiform activity is usually consistent within patients, suggesting that spike detection strategies that incorporate a patient-specific learning phase would be capable of lower error rates. Currently, the detection of interictal spikes and other epileptiform activity in clinical ECoG data is almost always carried out manually by trained neurologists. This introduces considerable variability in the accuracy of spike detection from reviewer to reviewer. The problem is further complicated by the lack of a consensus among neurologists on the features which define a spike. Discrepancies in review are explained by subjective variance between neuologists. In this study, we demonstrate a clustering based interictal spike detection algorithm. This algorithm improves upon an earlier method of creating patient-specific pattern matching templates by clustering the results of a generic pattern matching analysis (Nonclerq et al., 2010). This method was extended by expanding the generic pattern matching step and the clustering method. Further analysis examined the improvements in detection performance brought about by comparing signals from multiple electrodes in spike detection. This improved algorithm was evaluated using hippocampal ECoG recordings from epilepsy patients.

Disclosures: **S. Meisenhelter:** None. **P.C. Horak:** None. **A. Connolly:** None. **B. Jobst:** None.

Poster

829. Data Analysis: Human and Networks

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Topic: G.07. Data Analysis and Statistics

Support: NIDA Grant DA018310

Title: Understanding the impact of drugs of abuse and behavioral training using novel peptidomic assays

Authors: ***B. SOUTHEY**[1], X. CHEN[2], P. A. MORRIS[1], A. E. MAKI[1], P. E. GOLD[4], S. L. RODRIGUEZ ZAS[3], J. V. SWEEDLER[2];
[2]Chem., [3]Animal Sci., [1]Univ. of Illinois At Urbana-Champaign, Urbana, IL; [4]Dept. of Biol., Syracuse Univ., Syracuse, NY

Abstract: A microdialysis peptidomic experiment was conducted on 11 adult male Sprague Dawley rats to characterize the impact of drugs of abuse and behavioral training on endogenous peptides in the hippocampus as well as peptide release as monitored via *in vivo* micro-dialysis. Rats were subcutaneously injected with either saline or morphine (5 mg/kg) and were then trained or untrained on a spontaneous alternation. Peptides were extracted from each rat and analyzed using an 11 Tesla linear trap quadruple Fourier Transform Mass Spectrometer. The resulting tandem mass spectra were annotated using ProSight PTM. Spectral counting is a label-free semi-quantitative proteomics method that measures peptide abundance as the number of times a peptide is identified in tandem mass spectrometry spectra. This count data can only take zero and whole positive numbers. Furthermore, zero inflation (where there are a large number of zero counts than would be expected) can occur because not all peptides are detected in all samples. Generalized linear models are used to analysis discrete variables and address the problems associated with zero-inflation and overdispersion. Using a false discovery rate adjusted ProSight PTM p-value threshold of 0.0001, 1482 peptides including post-translational modifications were detected across all samples. The most frequent proteins included: polyubiquitin-B (768 peptides detected), thymosin beta-4 (173 peptides detected) and fibroblast growth factor (137 peptides detected). Peptide spectral counts were analysis using Poisson, zero-inflated, hurdle and truncated Poisson models as well as the Negative Binomial counterparts. The analysis of multiple models with different distributional assumptions identified many cases where the significant differences was due to the failure of a particular model to account for the zero-inflation and/or any overdispersion. For example, a polyubiquitin-B peptide exhibited a highly significant effect ($P < 0.001$) in models without overdispersion; however the same peptide only exhibited marginally significant differences (P-value < 0.1) using models with overdispersion. Significantly differential abundant peptides included: a SMG1 phosphatidylinositol 3-kinase-related kinase peptide that was 12 times more abundant with morphine than saline ($P<0.05$) and two thymosin beta-4 peptides were approximately 2.2 times more frequent with training than without training ($P<0.05$). These results exhibit the combination of proteomics and statistical methods for effective analysis of neuroscience experiments.

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Poster

829. Data Analysis: Human and Networks

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Program#/Poster#: 829.08/DD15

Topic: G.07. Data Analysis and Statistics

Support: NIH R01DC014085

Title: Dynamic estimation of human brain's receptive fields with confidence intervals

Authors: *S. AKRAM, J. Z. SIMON, B. BABADI;
Univ. of Maryland, College Park, MD

Abstract: One of the most important problems in computational neuroscience is to characterize the brain function using neural activity recorded from the brain in response to sensory inputs with statistical confidence. Most of existing estimation techniques, such as those based on reverse correlation, exhibit two main limitations: first, they are unable to produce dynamic estimates on par with the sampling resolution of neural data, and second, they often require heavy averaging across time as well as multiple trials in order to construct statistical confidence intervals for a precise interpretation of data. In this study, we address the above-mentioned issues for estimating auditory temporal receptive fields (TRF) as a parametric computational model for selective auditory attention in competing-speaker environments. In this case the TRF, which describes the way in which the neural response encodes an acoustic envelope, can be described mathematically as a sparse kernel, which regresses auditory MEG data with respect to the envelopes of the speech streams. We develop an efficient estimation technique by exploiting the sparsity of the TRF and adopting an l1-regularized least squares (SPARLS) estimator. This technique is capable of producing dynamic TRF estimates as well as confidence intervals at sampling resolution from single-trial MEG data. We evaluate the performance of our proposed estimator using evoked MEG responses from the human brain in an auditory attention experiment with two competing speakers. In the experiment, subjects are asked to stay attended to a target speaker for the first half of each trial (~ 30 seconds) and switch their attention to the masker speaker for the rest of the trial. The TRFs are estimated dynamically over time using the proposed technique, which reveal a precise characterization of the modulation of M50 and M100 evoked responses with respect to the attentional state of the subject at multi-second resolution.

Disclosures: **S. Akram:** None. **J.Z. Simon:** None. **B. Babadi:** None.

Poster

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Topic: G.07. Data Analysis and Statistics

Support: NIH Grant U54HG008540

James S. McDonnell Foundation

Title: Resting state fMRI identification of communicating sub-regions in the human medial temporal lobe

Authors: *R. SANCHEZ ROMERO[1], J. D. RAMSEY[1], J. C. LIANG[2], C. GLYMOUR[1]; [1]Philosophy, Carnegie Mellon Univ., Pittsburgh, PA; [2]Psychology, Univ. of Toronto, Toronto, ON, Canada

Abstract: Introduction: Connectivity analyses depend on building ROIs signals as averages of individual voxels. This average implies a loss of functional and anatomical information about sub-regions of voxels that drive high-level ROI connectivity. To recover this information, we present a statistical search method that analyze voxelwise conditional independence relations to identify sub-regions of voxels within a pair of effectively connected larger ROIs that are responsible for exchanging signals between those ROIs. We illustrate the method for rs-fMRI of medial temporal lobe (mtl) of a single human subject. Methods: High-resolution rs-fMRI of a single subject, 10 min scan, TR=1160ms, voxel size=2.4x2.4x2mm. ROIs in the mtl were defined manually according to procedures of the Preston Lab. at U.Texas at Austin. ROIs were defined for subiculum, CA1, CA23DG, entorhinal, perirhinal and parahippocampal cortex. To avoid high dimensionality statistics we concatenated ten sessions and applied our method to the concatenated dataset. Our method tests the independence of each pair of voxels, one from each of a pair of ROIs, R1, R2, that are directly causally connected, conditional on all voxels in any other ROIs that according to the given causal graph may influence voxels in both R1 and R2. For a voxel v in R1, the number of voxels in R2 that are found to be significantly associated with v is counted. This number is the R2 connection number for v in R1. Similarly for the R1 connection number for v in R2. The connection numbers of all the voxels in R1 and R2 are aggregated and partitioned into 2 sets using k-means. One set corresponds to highly connected voxels and the other to voxels with low or no connections in the R1-R2 pair. Locations of the voxels in the highly connected set yield the R1-R2 communication sub-region. This procedure is repeated for each pair of ROIs that are causally connected. We consider as the given causal graph the well-known medial temporal lobe structural connectivity circuitry. Results: We recovered sub-regions within larger ROIs of entorhinal cortex, CA1, CA23DG and subiculum. The sub-regions show robust spatial coherence and are in agreement with previous tractography-based structural connectivity results. We also tested our method on a simulated incorrect co-registration case that may arise when multiple scans are concatenated, and recovered sub-regions qualitatively similar to those obtained when simulated scans were correctly co-registered. Conclusions: Resolution of ROIs into voxelwise communication sub-regions allows us to recover important functional and anatomical information that bring us closer to understand the causal role of neural complexes.

Disclosures: **R. Sanchez Romero:** None. **J.D. Ramsey:** None. **J.C. Liang:** None. **C. Glymour:** None.

Poster

829. Data Analysis: Human and Networks

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Program#/Poster#: 829.10/DD17

Topic: G.07. Data Analysis and Statistics

Support: NIH Grant U54 EB020403

Title: 3-D tract-based regression analysis of white matter abnormalities in Alzheimer's disease

Authors: ***Y. JIN**[1,3], C. HUANG[2], D. SHEN[1], H. ZHU[2], P. M. THOMPSON[3]; [1]Radiology, [2]Biostatistics, Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [3]Neurol., USC, Los Angeles, CA

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disease that causes cognitive decline and affects millions of people worldwide. Diffusion weighted imaging (DWI) is an effective non-invasive method to yield information on white matter (WM) tract abnormalities caused by AD. Unlike traditional studies using the regional average measures or statistics from the "skeleton" of the WM, we examined the AD effects on the reconstructed 3-D profiles of major WM tracts. We analyzed baseline DWI data from 200 participants from the ADNI database (mean age: 73.2+/-7.5 SD; 116M/84F), consisting of 49 normal elderly people (NC), 111 with mild cognitive impairment (MCI), and 40 AD patients. Whole-brain tractography was performed. We manually constructed five WM tract atlases and applied a multi-atlas label fusion algorithm to extract 18 major WM tracts per subject. Next, we implemented a point-wise matching scheme to match fiber points across the population. Finally, we conducted a multivariate varying coefficient model to characterize the association between diffusion properties of tracts, such as fractional anisotropy (FA) and mean diffusivity (MD), and diagnostic status, with age and sex as covariates. Pointwise regression analysis was performed. Fig. 1 shows the 3-D MD profiles of three tracts affected by AD, the left and right cingulum and fornix, for groupwise comparisons. Each point's color represents the significance of difference between two groups based on the false discovery rate (FDR) corrected p-values (thresholded at 0.05). Comparing NC vs. MCI shows little difference in MD values in both cingulum tracts. As the disease progresses, the posterior portion demonstrates greater difference. Multiple regions in the fimbria and body of the fornix show degeneration even at the MCI stage and it spreads to the entire tract at the AD stage. The MD values of the AD group in all three tracts are higher. The 3-

D FA profiles between groups show less difference than those of MD, so MD may be a better measure for detecting AD and provide additional information on the etiology of the disease.

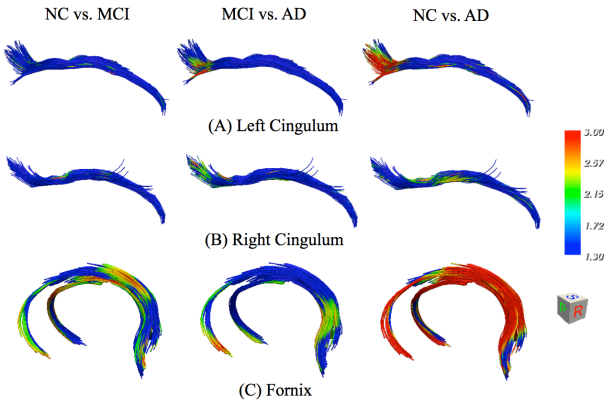

Fig. 1. 3-D tract profiles of left/right cingulum and fornix reveal difference in MD values among groupwise comparisons within the three diagnostic groups. The $-\log_{10}$ p-values are shown corresponding to the color bars. Results are FDR corrected across all points on each tract tested, thesholded between 1.3 (p=0.05) and 3 (p=0.001). Redder colors show greater group differences. The viewing direction is marked in the cube on the right (R-Right, P-Posterior, S-Superior).

Disclosures: Y. Jin: None. **C. Huang:** None. **D. Shen:** None. **H. Zhu:** None. **P.M. Thompson:** None.

Poster

829. Data Analysis: Human and Networks

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 829.11/DD18

Topic: G.07. Data Analysis and Statistics

Title: Methods to remove motion artifact in resting state multi-echo fMRI data

Authors: *J. D. POWER[1], M. PLITT[2], P. KUNDU[3], P. BANDETTINI[2], A. MARTIN[2]; [1]Lab. of Brain and Cognition, NIMH, Natl. Inst. For Mental Hlth., Bethesda, MD; [2]NIMH, Bethesda, MD; [3]Mount Sinai Hosp., NYC, NY

Abstract: The study of correlations and dynamics among resting state fMRI timeseries is increasingly influential in cognitive neuroscience and clinical studies. fMRI timeseries partially and indirectly reflect neural activity, but they are also prominently influenced by multiple kinds of artifactual factors. Removing or at least minimizing these artifactual influences on fMRI signals is of clear importance for drawing accurate inferences from such data. Over the last five years it has become apparent that some lifespan and clinical resting state fMRI effects can be attributed to unremoved motion artifact. New approaches and better validation of existing

approaches are needed to establish the validity of resting state findings. Recently, several groups have begun collecting “multi-echo” fMRI data in the hope that such data can be more thoroughly denoised than traditional “single-echo” fMRI data. Here, we examine 89 “multi-echo” datasets for evidence of motion artifact. These data are obtained from typical adults using sequences already described (Kundu et al., 2013) and are analyzed following procedures and logic outlined in (Power et al., 2015) and (Kundu et al., 2013). Motion artifact is present in the raw data and its properties are similar to those reported in prior studies. Multi-echo independent component analysis (ME-ICA), when applied to these data, removes some but not all influences of motion. After ME-ICA, global artifactual influences remain that are clearly artifact. An additional novel procedure, termed “godec”, is introduced to separate these more global signals from sparser signals. After removing the more global signals, motion dependence in the data is reduced to nearly undetectable levels (Figure 1). Although further demonstrations of the technique in other datasets are warranted, ME-ICA+godec appears to be a promising method of removing motion-dependent properties from resting state fMRI data.

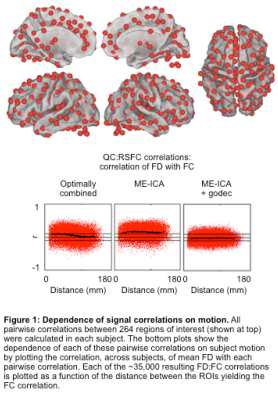

Figure 1: Dependence of signal correlations on motion. All pairwise correlations between 264 regions of interest (shown at top) were calculated in each subject. The bottom plots show the dependence of each of these pairwise correlations on subject motion by plotting the correlation, across subjects, of mean FD with each pairwise correlation. Each of the ~35,000 resulting FD:FC correlations is plotted as a function of the distance between the ROIs yielding the FC correlation.

Disclosures: J.D. Power: None. **M. Plitt:** None. **P. Kundu:** None. **P. Bandettini:** None. **A. Martin:** None.

Poster

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Topic: G.07. Data Analysis and Statistics

Title: Scalable human EEG: Task-motivated alignment of volitional behaviors reduces variability and enables population neurophysiology

Authors: *T. A. NICK, L. M. BERMAN, A. Z. BARNEHAMA;
Neurosci., DAQRI, Los Angeles, CA

Abstract: Human studies are difficult to control, leading to a heavy focus on time- and labor-intensive clinic and laboratory studies. These studies have illuminated numerous robust biological processes that can be studied using brief recordings of human subjects that may be stressed, uncomfortable, and unmotivated. However, behavioral and physiological processes that shift in response to the laboratory environment or that vary with daily or longer cycles according to biological pressures and rhythms are less well understood. We have developed a set of feedback tasks on mobile devices that, in concert with our wearable electroencephalography (EEG) headband, encourage users to actively participate in field studies through instant reinforcement using sensory cues that are derived from real-time analysis of behavior. A cloud analytics pipeline and database were built to provide longitudinal reports to users. We mined these de-identified data to compare tasks with associated behaviors and neural activity from >8,000 recording sessions and >600 unique users. Here we report that at least two behaviors, facial muscle activity and eye blinks, appear to be shaped by mobile application tasks (Percent time with muscle activity, positive-reinforcing task vs all others [Wilcoxon signed rank with N = 524 users]: $p < 3e-16$; Eye Blinks, gaze fixation vs a neutral task [Wilcoxon with N = 460 users]: $p < 7e-14$). This shaping occurred in users with little or no instruction on how to use the EEG headband or the mobile app, suggesting that this technology is easily scalable. Further, variation in these behaviors during a gaze fixation task was less than during a neutral task (Flinger-Killeen, $p < 0.002$ for each behavior). Next, we examined whether we could observe neural activity patterns in the data despite no exclusion or segregation of subjects based on age, gender, race, or other trait. We focused on a gaze fixation task that discourages eye blinks (see above). We found changes in brain oscillation that previously have been quantified only under highly controlled laboratory conditions with limited subject diversity (e.g., Cummings et al, 2000). Our preliminary data suggest that task-motivated alignment (TMA) of user behavior mimics laboratory control and enables scalable monitoring of diurnal neural activity patterns. For example, theta increased during the day (morning vs evening; Flinger-Killeen, $p = 0.19$; paired t-test with N = 107 users: $p < 0.027$). Therefore, TMA could provide a mechanism for decreasing behavioral variability and enhancing experimental control in human field studies, enabling scalability of clinical trials, research studies, and user-tailored feedback.

Disclosures: **T.A. Nick:** A. Employment/Salary (full or part-time):; DAQRI. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); DAQRI. **L.M. Berman:** A. Employment/Salary (full or part-time):; DAQRI. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); DAQRI. **A.Z. Barnehama:** A. Employment/Salary (full or part-time):; DAQRI. E. Ownership Interest (stock, stock options,

royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); DAQRI.

Poster

829. Data Analysis: Human and Networks

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 829.13/DD20

Topic: G.07. Data Analysis and Statistics

Title: Predicting quality of life and functional independency after stroke using supervised machine learning

Authors: M. BRANSCHEIDT[1], B. ZENKO[2], J. CERNY[1], *A. R. LUFT[1], C. GLOBAS[3]; [1]Univ. Zurich, Zurich, Switzerland; [2]Dept. of Knowledge Technologies, Jozef Stefan Inst., Ljubljana, Slovenia; [3]Univ. of Zurich, Zurich, Switzerland

Abstract: Prediction of stroke specific health outcome is essential but complex. With higher long-term survival there is rising interest for multidimensional assessment tools that reflect the impact of stroke on various aspects of life and for more accurate long-term prognostic models. The availability of high volume data sets is promising in this regard but poses new requirements to analyzing methods. We aimed to identify predictors for stroke specific quality of life evaluated by the Stroke Impact Scale (SIS) and for functional independence evaluated by the Extended Barthel index (EBI) using a machine learning approach. Clinical, neuropsychological and imaging data of 79 stroke patients (mean age 63.7 ±15.7, 29 females) from the Zürich Registry of Rehabilitation Outcomes were prospectively collected in the acute stage, at discharge from hospital and one year after stroke. Supervised machine learning with a decision tree algorithm was used 1) to describe the predictive value of 15 variables for the two outcome measures (SIS and EBI) and 2) to describe the impact of 14 variables at 12 months on SIS and EBI. Regarding the parameters collected in the acute stage, age, modified Rankin Scale (mRS) and the National Institute of Health Stroke scale (NIHSS) scores at discharge from hospital predicted SIS outcome (correlation coefficient 0.72). At 12 months the variables correlating with SIS outcome were mRS, NIHSS, Becks depression index (BDI), neglect and Berg balance scale (BBS) (correlation coefficient 0.85); BBS showing the highest relative predictive weight. For the prediction of the EBI outcome, we found different variable associations for two patient groups depending on mRS at discharge: for patients with mRS $\leq$3 the predictive variables were BMI, Fugl-Meyer-Assessment for the upper extremity (FM-UE), Early Rehabilitation Barthel Index (ERBI), NIHSS and mRS; for patients with mRS $\geq$ 4, NIHSS was not predictive for the later

functional outcome and ERBI and BMI had a higher main contribution compared to patients with lower mRS at discharge (correlation coefficient 0.63). At 12 months EBI scores correlated with BBS and the modified Ashworth scale (MAS) (correlation coefficient 0.74), again with BBS having a markedly higher main contribution. Machine learning using a decision tree algorithm can create complex but easy to interpret predictive models for functional independence and quality of life after stroke. These next-generation analytics might be particularly advantageous to elucidate the complex interactions between variables and multidimensional outcome measures that are increasingly applied in stroke rehabilitation.

Disclosures: **M. Branscheidt:** None. **B. Zenko:** None. **J. Cerny:** None. **A.R. Luft:** None. **C. Globas:** None.

Poster

829. Data Analysis: Human and Networks

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 829.14/DD21

Topic: G.07. Data Analysis and Statistics

Support: ERC Starter Grant SPEED

Title: Explicit modelling of the hemodynamic response in linking cognitive computational models to fMRI data

Authors: *G. DE HOLLANDER[1], S. D. BROWN[3], B. U. FORSTMANN[2];
[2]Psychology, [1]Univ. of Amsterdam, Amsterdam, Netherlands; [3]Fac. of Sci. and Information Technology, Sch. of Psychology, Univ. of Newcastle, Newcastle, Australia

Abstract: The past 10 years have seen a surge of studies that try to link computational, formal models of cognition, rooted in behavioral fields such as mathematical psychology and reinforcement learning, to neural measurements in humans. This is usually done with fMRI and has been called “model-based neuroimaging”. The model-based neuroimaging approach provides a way of increasing sensitivity to neural representations of latent cognitive processes and variables, such as evidence accumulation and stimulus-value. It also offers a way of testing the possible implementations of models of cognition. These models are usually validated in pure behavioral data, but say little about their implementation in the human brain. By far the most popular approach in model-based neuroscience is the regression-approach: a general linear model (GLM) is set up that includes a regressor corresponding to an estimated parameter of the model, convolved with a canonical hemodynamic response function. The GLM is fit to all voxel

timecourses in the brain, searching for brain areas where functional activity correlates with the parameter-of-interest as estimated by the cognitive model. This model is simplistic, because it assumes that the correlate of the parameter-of-interest in the BOLD-signal is nothing more than a linearly scaled canonical hemodynamic response function. Simple plots of the raw HRF signal during a speed-accuracy-tradeoff task in relevant areas show that not only the height of the response, but also the onset-to-peak and dispersion are modulated by the experimental manipulation. Here, we propose a joint-modeling-approach, where multiple aspects of the shape of the HRF are jointly estimated with the cognitive model using Markov Chain Monte Carlo sampling in a Bayesian setting. We applied the approach to fMRI data in a speed-accuracy-tradeoff task and show that it increases sensitivity while providing insight in the role of cortico-basal ganglia networks during speeded decision making

Disclosures: G. De Hollander: None. **S.D. Brown:** None. **B.U. Forstmann:** None.

Poster

829. Data Analysis: Human and Networks

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 829.15/DD22

Topic: G.07. Data Analysis and Statistics

Support: Boston Children's Hospital Faculty Career Development Award

Title: Automatic sulcal labeling and quantitative pattern analysis in the fetuses with brain malformations

Authors: *K. IM[1,4], A. GUIMARAES[5], Y. KIM[1], B. GAGOSKI[1,4], C. ROLLINS[4,2], E. YANG[4,3], P. GRANT[1,4];
[1]Div. of Newborn Med., [2]Neurol., [3]Radiology, Children's Hosp. Boston, Boston, MA; [4]Harvard Med. Sch., Boston, MA; [5]Faculdade de Medicina da USP, Sao Paulo, Brazil

Abstract: Defects in neurodevelopmental associated with many brain disorders result in disrupted global patterns of sulcal folding, which may emerge in early fetal life. For an advanced analysis of early sulcal folding development, this study aims to automatically label early primary sulci and investigate their patterns from T2 weighted MRI in 10 normal fetuses (21 – 28 weeks gestational age) and 6 fetuses with brain abnormalities (20 – 30 weeks). Fetal head motion in the raw image was corrected and isotropic high-resolution image volumes (0.75 × 0.75 × 0.75 [mm]) were reconstructed. Cortical plate area was semi-automatically segmented and 3D inner cortical plate surface was reconstructed using the isosurface function. Sulcal catchment basins were

identified on the cortical plate surface and previously published 9 fetal brain templates (23 – 31 weeks) were also used and processed as a reference for sulcal labeling and pattern analysis. We automatically labeled the sulcal basins and simultaneously quantified the global sulcal pattern similarities to the templates for individual fetal brains by matching with the templates using multivariate geometric features (relative 3D position, normalized surface area, and mean sulcal depth) and their inter-sulcal relationships and the prior knowledge of the spatio-temporal sulcal patterns. The sulcal pattern similarities to the normal templates were statistically compared between normal and abnormal fetuses using the Mann-Whitney *U* test. Our quantitative method optimized for the fetal brain showed the high accuracy and reliability of the automatic labeling and revealed significantly reduced sulcal pattern similarities to the normal templates in the fetal group with brain abnormalities, compared to the normal group (similarity to the template in the left, normal [mean ± SD]: 0.821 ± 0.018, abnormal: 0.754 ± 0.037 [$p < 0.001$], right, normal: 0.812 ± 0.022, abnormal: 0.762 ± 0.065 [$p = 0.039$]). Furthermore, it showed higher sensitivity in detecting individual's abnormality than qualitative fetal MRI assessment and reported abnormal sulcal pattern that might be compensatory or secondary to other brain abnormalities, but not qualitatively perceived. This study provides the potential to perform various regional analyses following sulcal labeling and to catch early signs of abnormal cortical growth from individual fetal brains.

Disclosures: **K. Im:** None. **A. Guimaraes:** None. **Y. Kim:** None. **B. Gagoski:** None. **C. Rollins:** None. **E. Yang:** None. **P. Grant:** None.

Poster

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 829.16/DD23

Topic: G.07. Data Analysis and Statistics

Support: DP2-OD006454

Title: Quantitative analysis of sleep neural dynamics

Authors: ***M. J. PRERAU**[1], M. T. BIANCHI[2], P. L. PURDON[1];
[1]Anesthesia, Critical Care, and Pain Med., Massachusetts Gen. Hosp., Charlestown, MA;
[2]Neurol., Massachusetts Gen. Hosp., Boston, MA

Abstract: Sleep is a continuous, dynamic process involving the complex interaction of cortical and sub-cortical networks within the brain, which operate on multiple time scales. Study of the

sleep electroencephalogram (EEG) is therefore an ideal, natural means of simultaneously observing the correlates of activity from numerous brain regions. While the past 50 years have seen extraordinary advances in our understanding of the physiological mechanisms underlying sleep, current analyses still rely heavily on sleep staging, a subjective process using visual inspection to discretize sleep into semantically-defined stages (e.g. Wake, REM, NREM 1-3) using 30-second epochs. The activity within these stages is assumed to be stationary, with instantaneous transitions between them. As a consequence, sleep staging greatly oversimplifies the true signal dynamics and thus does not fall in line with the observed evolution of the data. We develop novel computational techniques to capture the full dynamic nature of the sleep EEG, thereby more accurately representing our knowledge of the underlying neurophysiology, while providing a robust statistical framework for characterizing sleep.

Disclosures: **M.J. Prerau:** None. **M.T. Bianchi:** A. Employment/Salary (full or part-time):; The Milton Foundation, The Center for Integration of Medicine and Innovative Technology. F. Consulting Fees (e.g., advisory boards); GrandRounds, Foramis, Servier. **P.L. Purdon:** None.

Poster

829. Data Analysis: Human and Networks

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 829.17/DD24

Topic: G.07. Data Analysis and Statistics

Title: Reciprocal couplings and their modes in eye contact

Authors: *R. LEE;
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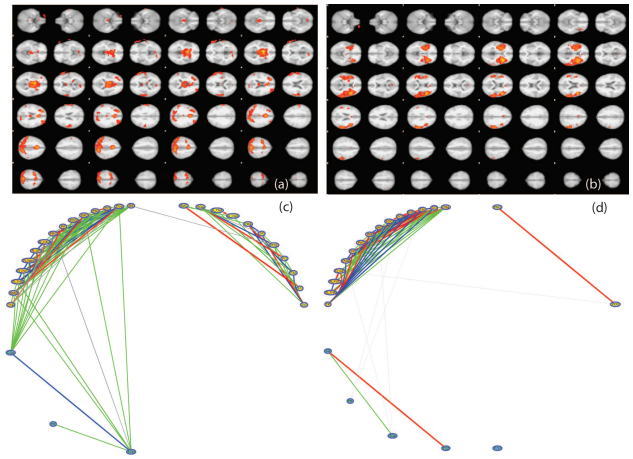
Abstract: Eye contact recruits multiple brain processes. Some of them are reciprocal, while others are non-reciprocal. With dyadic fMRI (dfMRI) [1], many of these interactive processes can be identified in a data-driven approach, and entwinement between reciprocal and non-reciprocal responses can be untwined by the dual logic theory (DLT) [2]. The fusion of dfMRI and DLT results in a cerebral coordinate for reciprocal interaction (CCRI). In this study, 19 dyadic datasets for eye contact are decomposed by group ICA [3]. The independent components (IC) with dyadic responses and eye-contact rhythm are selected and projected to the CCRI, and yield reciprocal coupling modes [2]. Each coupling mode is parcellated by anatomical structures based on Harvard-Oxford atlas in FSL. The activated parts of the parcellations are served as regions-of-interest (ROI) to extract the average time series from each dyadic dataset. For each dataset, correlations between all the time series are calculated, but only the correlations with

p<0.05 are selected. For all 19 datasets, the average correlations are selected by z-test with 95% chance and threshold 0.1, which become the connectivity of the given mode. Currently ten coupling modes are identified. Two of the ten modes are illustrated in Fig. 1 where a & b are their IC, and c & d are their connectivity. In Fig. 1 c & d, the right and left side labels are for right and left side subjects, upper and lower part labels are for the exogenous and endogenous systems. For the 1st mode in Fig. 1c, left subjects' brainstem is coupled with right subjects' postcenter gyrus (POG), and the exogenous coupling emerges to endogenous precuneus. For the 2nd mode in Fig. 1 d, left subjects' pallidum is coupled with right subjects' POG, and the exogenous coupling emerges to endogenous angular gyrus. The reciprocal coupling modes reveal the parallel processes during dyadic interaction. It set forth an approach to analyze social interaction. [1] Lee RF, et al (2012): Magn Reson Med 68(4):1087-96. [2] Lee RF. (2015): PLoS One 10(4):e0121791. [3] Beckmann CF, et al (2004): IEEE Trans Med Imaging 23(2):137-52.



Disclosures: **R. Lee:** None.

Poster

829. Data Analysis: Human and Networks

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 829.18/DD25

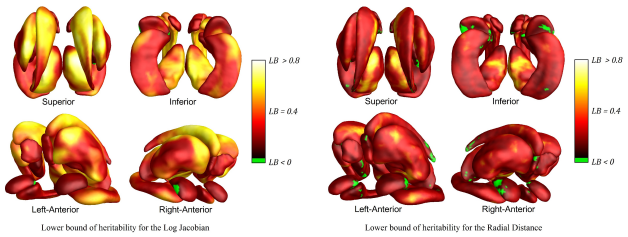
Topic: G.07. Data Analysis and Statistics

Support: NIH Grant U54 EB020403

Title: Mapping subcortical shape heritability to empower genetic association studies

Authors: *B. GUTMAN[1], N. JAHANSHAD[2], P. K. DOUGLAS[3], P. M. THOMPSON[2]; [1]Inst. for Neuroimaging and Informatics, IGC - Univ. of Southern California, Marina Del Rey, CA; [2]Imaging Genet. Ctr., USC, Los Angeles, CA; [3]Neurol., Univ. California Los Angeles, Los Angeles, CA

Abstract: Imaging Genetics is the study of genetic associations with imaging biomarkers. Its relevance to our understanding of the brain has been demonstrated recently [1]. In a number of previous imaging genetics studies, subcortical regional volumes have been traditionally used as the standard image-derived measures. While reducing the multiple comparisons burden to a manageable size, this approach overlooks subtleties of sub-regional shape differences. In this work, we choose instead to analyze the entire shape complex of the basal ganglia and limbic system at a fine scale. We present a multi-cohort shape heritability study, extending the fast spherical demons registration to subcortical shapes via medial modeling. A multi-channel demons registration based on vector spherical harmonics is applied to medial and curvature features, while controlling for metric distortion [2]. We registered and compared seven subcortical structures of 1480 twins and siblings from the Queensland Twin Imaging Study and Human Connectome Project: Thalamus, Caudate, Putamen, Pallidum, Hippocampus, Amygdala, and Nucleus Accumbens. Radial distance and tensor-based morphometry (TBM) features were found to be highly heritable throughout the entire basal ganglia and limbic system. Surface maps reveal subtle variation in heritability across functionally distinct parts of each structure. Medial Demons reveals more significantly heritable regions than two previously described surface registration methods. This approach may help to prioritize features and measures for genome-wide association studies. 1.Hibar DP, et al.: Common genetic variants influence human subcortical brain structures. Nature 2015:In Press. 2.Gutman B, et al.: Registering Cortical Surfaces Based on Whole-Brain Structural Connectivity and Continuous Connectivity Analysis. In: Medical Image Computing and Computer-Assisted Intervention - MICCAI 2014. Volume 8675, 2014: 161-168.



Disclosures: **B. Gutman:** None. **N. Jahanshad:** None. **P.K. Douglas:** None. **P.M. Thompson:** None.

Poster

829. Data Analysis: Human and Networks

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 829.19/DD26

Topic: G.07. Data Analysis and Statistics

Title: Distributed anatomical substrates identified by pattern classification predict cortical excitability and inhibition

Authors: *E. DAYAN[1], V. LÓPEZ-ALONSO[2], S.-L. LIEW[3], L. G. COHEN[4];
[1]Human Cortical Physiol. Section, NINDS/NIH, Bethesda, MD; [2]Univ. of A Coruña, A Coruña, Spain; [3]USC, Los Angeles, CA; [4]NINDS, NIH, Bethesda, MD

Abstract: Motor evoked potentials (MEPs), elicited by single-pulses of transcranial magnetic stimulation (TMS) over the primary motor cortex, are a well-regarded measure of cortical excitability. Similarly, short interval intracortical inhibition (SICI), elicited by paired-pulse TMS, is widely used as a protocol for measuring cortical inhibition. These two TMS protocols have been highly instrumental in probing the physiological characteristics of the central nervous system, and are often used to quantify plastic changes induced by noninvasive brain stimulation techniques such as transcranial direct current stimulation. Still, MEPs and SICIs clearly differ among subjects, and the origins of this variability remain poorly understood, often being attributed to spontaneous and transient factors such as fluctuations in corticospinal excitability. Here, we evaluated whether inter-individual variability in MEPs and SICIs may also originate from more stable factors like individual variability in brain structure. High resolution structural magnetic resonance imaging scans were collected in a group (n=25) of healthy volunteers for whom- in a separate session-TMS with single and paired pulses was administered to record MEPs and SICIs respectively. Support vector machine (SVM) pattern classification was then used to train a classifier to distinguish between subjects who had lower and higher MEPs and SICIs, based on their segmented gray-matter images. Testing of the classifier's performance revealed that distributed patterns of gray-matter volume, extending beyond motor regions allowed for an accurate and significant classification of MEP and SICI amplitudes. These results suggest that variability in TMS-elicited cortical excitability and inhibition may partially originate from subjects' brain anatomy.

Disclosures: **E. Dayan:** None. **V. López-Alonso:** None. **S. Liew:** None. **L.G. Cohen:** None.

Poster

829. Data Analysis: Human and Networks

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 829.20/DD27

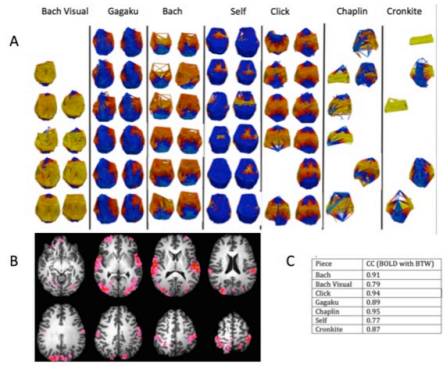
Topic: G.07. Data Analysis and Statistics

Support: Ting Tsung and Wei Fong Chao Foundation

Title: Correlation between bold activation and centrality in fmri connectivity when listening to music

Authors: *C. KARMONIK[1,2], J. ANDERSON[1], A. BRANDT[3], F. BROOKS[2], J. FRAZIER[2]; [1]Houston Methodist Res. Inst., Houston, TX; [2]Ctr. for Performing Arts Med., Houston Methodist Hosp., Houston, TX; [3]Shepard Sch. of Music, Houston, TX

Abstract: Background: Listening to familiar music has recently been reported to induce beneficial changes during stroke recovery concurrently with increase of cortical thickness. To foster a better understanding of the neural correlates when listening to different music genres, fMRI BOLD activation from listening to different music genres was correlated with functional connectivity. Materials and Methods: Twelve healthy volunteers listened to seven different auditory pieces, two unfamiliar pieces (Bach invention #1, classical Japanese opera, Gagaku), one with visual guidance (Bach), one self-selected piece and three language pieces (African click language, emotional speech, Chaplin, and unemotional textbook reading, Cronkite). BOLD activation maps were derived and functional connectivity maps were created using a graph theoretical approach from which betweenness (BTW) was calculated as centrality measure. Centrality maps were built for individual subjects and averaged in Talairach space. Results: Distinct different BOLD activation maps and functional connectivity patterns were obtained for each audio piece but consistent amongst all subjects (figure 1). Bach and click language pieces exhibited more regions with increased blood flow during the listening periods as compared to the resting periods. This was reversed for Japanese opera and self-selected pieces. For both Chaplin and Cronkite textbook passages, activation was distinctively less and variable between the listening and resting period. Group-averaged maps correlated strongly and statistical significantly ($p<0.05$) for BOLD and BTW patterns (figure 1). Conclusion: Dynamic changes in fMRI connectivity are induced by listening to different music genres and spoken language. Strength of BOLD activation coincided with a centrality measure that identifies voxels with large influence on the transfer of information through the fMRI connectivity network.



Piece	CC (BOLD with BTW)
Bach	0.91
Bach Visual	0.79
Click	0.94
Gagaku	0.89
Chaplin	0.95
Self	0.77
Cronkite	0.87

Figure 1: A: Superior view of 3D graph network in anatomical space for the different auditory pieces for all subjects (top left to bottom right) colored by BOLD increase during listening (red/yellow: positive, blue: negative). **B**: Average BTW centrality map for self-selected music. **C**: Table of correlation coefficient (CC) for all auditory pieces between BOLD and BTW.

Disclosures: C. Karmonik: None. **J. Anderson:** None. **A. Brandt:** None. **F. Brooks:** None. **J. Frazier:** None.

Poster

829. Data Analysis: Human and Networks

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Topic: G.07. Data Analysis and Statistics

Support: NIH R43MH084358

NIH R01 DC007683

NIH R01 DC002852

NIH R01 DC013027

Title: Acceptable values of similarity coefficients in neuroanatomical labeling of MRI

Authors: *A. J. WORTH[1], J. A. TOURVILLE[2];
[1]Neuromorphometrics, Inc., Somerville, MA; [2]Dept. of Speech, Language, and Hearing Sci., Boston Univ., Boston, MA

Abstract: The delineation of neuroanatomy in magnetic resonance brain scans (known as segmentation, labeling or tracing) is commonly validated by comparison with a manually created gold standard. This is done using spatial overlap statistics such as the Dice index and Jaccard coefficient. We examine published similarity values for particular anatomical regions to

determine what is generally acceptable and compare this with results obtained by manually labeling repeat scans of 20 subjects. Each subject was scanned twice separated by some time and both scans were labeled independently. MRI brain scans were obtained from the "reliability" set in the Open Access Series of Imaging Studies (OASIS). A single highly trained technician used custom software “NVM” to create closed borders around regions with isointensity contours and editing. Labeling was performed using protocols that precisely define the landmarks, borders and methods for delineating anatomical regions. “SegMentor” scripts helped assure accuracy and documented adherence to the labeling protocols by imbedding them into the software. 72 regions comprehensively covered the brain including: cerebral and cerebellar gray and white matter, ventricles, brain stem, accumbens, amygdala, caudate, hippocampus, pallidum, putamen, and thalamus according to the “General Segmentation” protocol defined by the MGH Center for Morphometric Analysis, and the cortex was parcellated into 51 units based on 36 sulci according to the BrainColor protocol. An anatomist with years of labeling experience checked all results and the technician made corrections as necessary. We demonstrate that manual results can have the best possible overlap metrics, but only after spending a sufficient (and many would say excessive) amount of effort. The similarity coefficients we present thus represent a kind of upper bound on what is currently attainable. Similarity values occur over a range because specific anatomical regions have differing amounts of anatomical variation and are affected differently by scanning artifacts: some regions are harder to label than others because the boundaries are less apparent. Manual methods have the advantage that anything that can be seen by the human visual system can be labeled. But manual labeling is tedious, requires a lot of expertise, and can have errors due to fatigue and variation in the application of the labeling protocol. Automated methods require less human time/cost but fail on unfamiliar anatomy and need to be checked and corrected. We conclude with an argument as to why an optimal system involves interactive automation: a combination of algorithms along with manual checks and corrections.

Disclosures: **A.J. Worth:** A. Employment/Salary (full or part-time):; Neuromorphometrics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuromorphometrics, Inc. **J.A. Tourville:** F. Consulting Fees (e.g., advisory boards); Neuromorphometrics, Inc..

Poster

829. Data Analysis: Human and Networks

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 829.22/DD29

Topic: G.07. Data Analysis and Statistics

Support: Pervasive and Ambient Computing Lab, Loyola University Chicago

Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Brazilian Ministry of Education

Title: Real-time activity recognition graphical front-end display with semi-supervised labeling assistance

Authors: *I. RABKINA, L. L. NOGUEIRA, M. V. ALBERT;
Loyola Univ. Chicago, Chicago, IL

Abstract: Activity recognition is a valuable tool for both diagnosing motor impairments and measuring response to therapeutic interventions. We have developed a graphical user interface for interactively displaying activity recognition results in real-time. The system also provides off-line navigation and visualization of recorded sensor data, and assists in activity labeling using a semi-supervised machine learning approach. Traditionally, the primary means of evaluating activity recognition algorithms is through the relatively slow process of off-line analysis of pre-recorded data. The goal of this system is to provide real-time feedback to researchers and clinicians about the behavior of advanced activity recognition algorithms. Sensor readings including accelerations, torques, and magnetic field strength are collected using a wireless motion sensor worn on the waist (Shimmer3). The data is communicated via low-power Bluetooth to a client device which transmits it to a MySQL database in the cloud. If a trained activity recognition algorithm is provided, the system renders the sensor signals and inferred activity in real-time using a traditional client-side front-end architecture (JavaScript/jQuery/Flot). Using our system, data can also be labeled directly for use in training and validating recognition models. Uniquely, An iterative supervised learning approach is used to provide labeling suggestions which are updated as the user labels additional data. For this labeling, we use regularized logistic regression on a standard set of signal processing features used in activity recognition. Using the automatic labeling suggestions, real-time interactive demonstration, and off-line review, this system can help any lab streamline activity recognition algorithm training, validation, and acceptance; this can lead to better activity recognition for future personal, research, or clinical use.

Disclosures: I. Rabkina: None. **L.L. Nogueira:** None. **M.V. Albert:** None.

Poster

829. Data Analysis: Human and Networks

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 829.23/DD30

Topic: G.07. Data Analysis and Statistics

Title: Crosscorrelation analysis of prewhitened human connectome resting-state fMRI data: Interhemispheric effects in pre- and post-central areas

Authors: *P. S. CHRISTOVA, A. P. GEORGOPOULOS;
Dept Neurosci, Univ. Minnesota, Minneapolis, MN

Abstract: We used public, resting-state fMRI data of the NIH Blueprint Human Connectome Project (HCP; www.humanconnectome.org) to investigate the interactions between left and right pre-and post-central areas in 10 healthy right-handed subjects (2 mm isometric spatial resolution; temporal resolution = 0.72 sec; ~2,000 vertices per area above). For that purpose, first, we prewhitened the individual fMRI time series of each vertex using a (15,1,1) ARIMA model (Christova et al., True associations between resting fMRI time series based on innovations. J Neural Eng 8:046025, 2011) to obtain practically white noise innovations (residuals). We then calculated the crosscorrelation (CC) function (±30 lags = 21.6 s) between all innovations of left/right vertices in pre- and post-central areas (~4,000,000 crosscorrelograms per subject per area). Finally, we identified the lag where the absolute maximum CC occurred, retained the signed CC value, and transformed it to z = arctanh(CC) to normalize its distribution. We found the following. In 9 out 10 subjects, the left precentral cortex exerted a negative effect on the right one, as evidenced by a highly significantly lower mean z (across 30 lags) in the Left-to-Right half of the crosscorrelogram. In contrast, the right precentral cortex exerted a positive effect on the left one, as evidenced by a highly significantly higher mean z (across 30 lags) in the Right-to-Left half of the crosscorrelogram ($p < 0.001$, for all effects, t-test). (The direction of these effects was reversed in 1 subject.) The same highly significant effects were observed for the postcentral areas. These results demonstrate orderly interhemispheric interactions between pre-and post-central cortices that point to a negative feedback mechanism, probably serving to maintain a stable equilibrium.

Disclosures: **P.S. Christova:** None. **A.P. Georgopoulos:** None.

Poster

829. Data Analysis: Human and Networks

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 829.24/DD31

Topic: G.07. Data Analysis and Statistics

Support: NIH Grant EY022116

Title: An automated tool for parcellating human visual cortex in individual subjects based on functional imaging data

Authors: *N. C. BENSON[1], K. KAY[2], J. WINAWER[1];
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Abstract: One of the first tasks in the analysis of many neuroimaging experiments is the parcellation of the cortical surface into functional regions of interest (ROIs) based on experimental localizers, for example the labeling of V1, V2, and V3 based on retinotopic mapping data or the identification of the fusiform face area (FFA) based on cortical responses to faces. This task is time-consuming and prone to human bias; additionally, its difficulty increases as imaging resolution increases, as localizer experiments become more complex, and in cases where ROI boundaries are highly variable between subjects. Particularly in the case of large datasets, such as the Human Connectome Project (HCP), drawing individual ROIs by hand for hundreds of subjects represents a significant expense. These difficulties often lead researchers to rely on cortically aligned group-average data to represent or define ROIs despite poor alignment in many cortical areas. In order to compare results across laboratories and across subject populations (disease vs. control, children vs. adults, etc), it is essential to have well-justified and reproducible methods for defining ROIs in individual subjects. We have automated the process of labeling individual-subject ROIs by registering localizer data to simple boundary or map models projected onto the cortical surface. Our method allows researchers to incorporate group-average data into the labeling process as a prior while also respecting the functional data from the individual subjects. Moreover, multiple ROIs can be simultaneously defined in a template and jointly fit. We demonstrate this method first by labeling areas V1-V3 in 19 subjects with retinotopic mapping data. When V1-V3 maps were automatically defined using only half of the retinotopic data, the remaining eccentricity and polar angle values were predicted with a median absolute error of 0.7° and 20.3°, respectively. We then examine the face, place, body, and object data from 494 subjects in the HCP500 working-memory experiment and quantify the accuracy of fits to individual ROIs for faces, places, bodies, and objects based on automatically labeling. The ROIs are fit to individual brains in a large dataset despite the variation in cortical activation patterns between subjects. The use of a prior from a large set of group data makes the algorithm robust to noise in the individual functional data, while at the same time, incorporating the individual data allows the researcher to capture individual variations in ROIs. The tool and source code will be made publicly available. Because the tool is automated, it facilitates reproducible computation across studies and laboratories.

Disclosures: **N.C. Benson:** None. **K. Kay:** None. **J. Winawer:** None.

Poster

829. Data Analysis: Human and Networks

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 829.25/DD32

Topic: G.07. Data Analysis and Statistics

Title: Intrinsic connectivity between auditory and motor networks: Is it associated with sensory suppression during overt speaking?

Authors: ***V. G. VAN DE VEN**[1], L. WALDORP[2], I. CHRISTOFFELS[3], J. VAN DEN BOSCH[4], A. WALTHER[5], M. J. NAUMER[6];
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Abstract: During speaking, auditory cortex (AC) activity may be suppressed as the result of an internal copy of motor commands that is sent to sensory areas (efference copy). Recent incidental reports of auditory-motor functional connectivity during resting states suggest that sensory-motor interactions may occur before and beyond motor planning states. It is unknown if intrinsic sensory-motor connectivity is associated with task-related sensory suppression. In this study, we investigated this issue of auditory-motor connectivity during resting states and during overt speaking in two parts. In the first part, we used bilateral AC in a seed-based analysis to assess functional connectivity in resting state FMRI data of four independent studies. We found that AC was significantly connected to supplementary motor area (SMA) and dorsal anterior cingulate cortex, medial thalamic nuclei, right inferior frontal gyrus and sensorimotor cortical areas. In the second part, we investigated FMRI timeseries of two overt speaking studies with superimposed pink noise to mask speech feedback. AC-seeded functional connectivity of the fixation periods between task blocks showed similar results to the resting state studies. We then correlated the functional connectivity coefficients of fixation in non-auditory areas to task-based sensory suppression in bilateral AC. We found that stronger AC-SMA connectivity during fixation was associated with stronger sensory suppression in AC across individuals. These findings suggest that the intrinsic functional architecture of the human brain includes ongoing auditory-motor coupling, and that this intrinsic connectivity may contribute to task-based sensory suppression.

Disclosures: **V.G. Van de Ven:** None. **L. Waldorp:** None. **I. Christoffels:** None. **J. van den Bosch:** None. **A. Walther:** None. **M.J. Naumer:** None.

Poster

830. Data Analysis: Human

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 830.01/DD33

Topic: G.07. Data Analysis and Statistics

Support: CIHR

JS McDonnell Foundation

Title: Constructing the macaque connectome *in vivo* using diffusion weighted imaging: A comparison with tracer studies

Authors: ***K. SHEN**[1], A. GOULAS[2], J. GATI[3], R. MENON[3], A. R. MCINTOSH[1], S. EVERLING[3];
[1]Rotman Res. Inst., North York, ON, Canada; [2]Dept. of Computat. Neurosci., Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany; [3]Univ. of Western Ontario, London, ON, Canada

Abstract: Deriving structural connectivity using diffusion-weighted imaging (DWI-SC) methods has become especially popular across both the basic and clinical neurosciences. However, direct empirical validation of DWI-SC derived *in vivo* with SC derived using the current "gold standard" invasive tract tracing (TT-SC) technique is lacking, and a recent study that used DWI to estimate SC in macaques *ex vivo* has suggested that the neuroimaging technique may be severely limited (Thomas et al., 2014; but see Azadbakht et al 2015). In this study, we estimated SC using DWI and directly compared it to SC derived from invasive tracer studies. DWI data were collected using a Siemens 7T scanner from two macaque monkeys under light anaesthesia. Probabilistic tractography was performed for two parcellations: a single-hemisphere parcellation matching that reported in a recent comprehensive tracer study (Markov et al., 2014), and a whole-brain parcellation with SC derived from the CoCoMac database of tracer studies (Stephan et al., 2001). When curvature thresholds were set to recommended values (~80 deg), accuracy (proportion of correctly detected connections) was high for the single-hemisphere parcellation (.745) and better than the whole-brain parcellation (.517). Consistent with previous reports on probabilistic tractography, an ROC analysis revealed high sensitivity (.895) but low specificity (.173). Sensitivity dropped with increasing tract length and decreasing tract capacity, suggesting that DWI is limited in its detection of long and small tracts. Sensitivity and specificity, however,

were optimal at lower curvature thresholds (~65 deg), and tractography results were better matched to TT-SC when the weakest one-third of DWI-SC was discarded. Importantly, the topological features of the DWI-derived network mimicked that of the TT-derived one. Node degree was highly correlated between the two networks ($r = 0.6$, $p < 0.001$), and high-degree hubs identified in the DWI network were the same as those identified in the TT network. Moreover, the community structure of the two networks was highly overlapping, suggesting that the global topology of the macaque connectome is well captured by DWI techniques. Together, these data suggest that DWI is a valuable tool for understanding large-scale structural networks.

Disclosures: K. Shen: None. **A. Goulas:** None. **J. Gati:** None. **R. Menon:** None. **A.R. McIntosh:** None. **S. Everling:** None.

Poster

830. Data Analysis: Human

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 830.02/DD34

Topic: G.07. Data Analysis and Statistics

Title: Mixed effects for large datasets

Authors: *D. M. NIELSON[1], P. B. SEDERBERG[2];
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Abstract: Mixed effects models provide significant advantages in sensitivity and flexibility over typical statistical approaches to neural data analysis, but mass univariate application of mixed effects models to large neural datasets is computationally intensive. Threshold free cluster enhancement also provides a significant increase in sensitivity, but requires computationally-intensive permutation-based significance testing. Not surprisingly, the combination of mixed effects models with threshold free cluster enhancement and nonparametric permutation-based significance testing is currently completely impractical. Our mixed effects for large datasets (MELD) method combines the power of linear mixed effect regression with multivariate approaches for maximizing variance in the dimensions of interest. When evaluated on simulated data and with publically available fMRI data, MELD is more sensitive than standard techniques, such as element-wise general linear models followed by cluster correction.

Disclosures: D.M. Nielson: None. **P.B. Sederberg:** None.

Poster

830. Data Analysis: Human

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 830.03/DD35

Topic: G.07. Data Analysis and Statistics

Title: Man vs. machine: improving physical activity tracking in the presence of deceptive human behavior

Authors: *S. SAEB[1], K. KORDING[2], D. MOHR[3];
[2]Dept. of Physical Med. and Rehabil., [3]Dept. of Preventive Med., [1]Northwestern Univ., Chicago, IL

Abstract: Human activity tracking systems are intended to be used with normal, expected behavior. For example, tracking systems do not expect that humans will walk on their hands. As a result, people can trick activity trackers by performing any behavior that generates similar tracking results. For example, one can make a smartphone-based pedometer detect 'walking' or 'running' by simply shaking the phone with one's hands while sitting. In this study, we asked (1) to what extent users are capable of deceiving activity tracking systems, and (2) if these systems can be improved to detect deceptive behavior by using training data from intentionally deceptive behavior. To answer these questions, we asked 15 participants to try to deceive a phone-based activity classifier by making it detect 'walking' while they were seated, and making it detect 'sitting' while they were walking. The participants continuously received feedback about the detected activity, and were free to carry and move the phone in any way they preferred. If they succeeded in deceiving the classifier, we used their motion data (accelerometer and gyroscope sensors) to retrain the classifier, and asked them to challenge it again. Importantly, participants had to adapt after each retraining since the classifier learned about their previous deceptive behavior. The experiment continued until they could no longer deceive the classifier. We found that some participants were not able to deceive the classifier at all, while others succeeded in up to 5 rounds of retraining. We next asked whether a classifier trained on one individual's deceptive behavior improved the predictions of other individuals. Classifiers trained on normal activity data predicted true behavior (i.e., not the intended deception) with an accuracy of ~38%, while training on only one participant's deceptive behavior improved accuracy to ~62%. Interestingly, this improvement was not affected by whether the training samples were from a successful participant with multiple retraining sessions or unsuccessful ones with only one session. An implication of this study is that activity tracking systems can be significantly improved by including deceptive activity data from even a few individuals.

Disclosures: S. Saeb: None. **K. Kording:** None. **D. Mohr:** None.

Poster

830. Data Analysis: Human

Location: Hall A

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Program#/Poster#: 830.04/DD36

Topic: G.07. Data Analysis and Statistics

Title: The integrated pain quantification index (IPQI): a novel multi-domain index for measuring pain

Authors: *J. A. SHETAKE[1], S. LIN[2], N. MEKELBOBROV[2], J. NORTH[3], L. KAPURAL[3], M. WALLACE[4], E. GRIGSBY[5];
[1]Boston Scientific Neuromodulation, Santa Clarita, CA; [2]Boston Scientific Neuromodulation, Valencia, CA; [3]Carolinas Pain Inst. and Ctr. for Clin. Res., Salem, NC; [4]Ctr. for Pain Medicine, Univ. of California, San Diego, San diego, CA; [5]Napa Pain Inst., napa, CA

Abstract: Multi-site pain, including anatomical distribution, continuousness, and regional intensities, is a key challenge in neurostimulation treatment where pain relief depends heavily on capturing nerve fibers with highly diverse anatomical accessibility. We undertook the Multiple Areas of Pain (MAP) study to estimate the prevalence of multi-site pain in the spinal cord stimulator (SCS)-eligible pain patient population and to develop a quantitative and clinically relevant measure which captures the various aspects of multi-site pain in a single index. In this paper, we will present the methodological details of the Integrated Pain Quantification Index (IPQI), and its development and validation. The Multiple Areas of Pain (MAP) study is a multi-center epidemiological study of multi-site pain in the SCS-eligible, chronic pain patient population. The study included a total of 828 US subjects enrolled across 14 clinical sites. Patients were provided with body map drawings to capture the following 4 key dimensions of multi-site pain: distribution, continuousness, local average intensities, and local peak intensities. Each was collected at high resolution, for each one of 47 regions of the body. Principal Component Analysis (PCA) was used to assign relative weights to each component for its contribution to the index. Each subject's 47 regional IPQI scores were calculated and finally the overall IPQI score was calculated as the sum across all regions. The IPQI provides a single score ranging from 0-100, with 0 corresponding to no pain anywhere on the body and 100 corresponding to pain everywhere on the body at maximum intensities and at all times. Finally, validation assessments were collected across multiple health domains, including pain quality (McGill), disability (Oswestry, PDI), quality of life (EQ-5D-5L), depression (CES-D), anxiety (GAD-7), and productivity (WPAI:SHP), to validate the IPQI against well-established measures. The IPQI exhibited statistically robust behavior across all four of its component variables, and

can therefore be used as a single stand-in measure for all four assessments. Strong correlation was observed with multiple well-established assessments across several health-domains, validating the clinical relevance of this index. In light of the potential importance of multi-site pain for SCS patients, a comprehensive and robust measure is needed. The IPQI is a new measure that captures 4 keys dimensions of multi-site pain in a single score. This index is well-suited for characterizing the prevalence of multi-site pain in SCS patients, and is recommended as an analytical tool in future studies.

Disclosures: J.A. Shetake: A. Employment/Salary (full or part-time):; Boston Scientific Neuromodulation. **S. Lin:** A. Employment/Salary (full or part-time):; Boston Scientific Neuromodulation. **N. MekelBobrov:** A. Employment/Salary (full or part-time):; Boston Scientific Neuromodulation. **J. North:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Boston Scientific Neuromodulation. **L. Kapural:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Boston Scientific Neuromodulation. **M. Wallace:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Boston Scientific Neuromodulation. **E. Grigsby:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Boston Scientific Neuromodulation.

Poster

830. Data Analysis: Human

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 830.05/DD37

Topic: G.07. Data Analysis and Statistics

Support: Astra Zeneca Investigator Initiated Grant

Title: Skellify: a machine learning tool for classifying depression using DTI-based white matter skeletons

Authors: J. BENOIT[1], M. BROWN[1], A. GREENSHAW[1], S. DURSUN[1], *R. RAMASUBBU[2]; [1]Univ. of Alberta, Edmonton, AB, Canada; [2]Psychiatry/Clinical Neurosciences, Univ. of Calgary, Hotchkiss Brain Inst., Calgary, AB, Canada

Abstract: Background: Machine learning approaches are increasingly being used in the development of diagnostic and prognostic tools for Major Depressive Disorder (MDD). Differences in brain white matter shown by Diffusion Tensor Imaging (DTI) scans may serve as a proxy for MDD symptom severity. Here, machine learning methods were applied to DTI scans to examine the diagnostic accuracy of white matter integrity in predicting MDD symptom severity. Methods: Participants were fifty two medication-free patients with DSM-IV-defined MDD, and eighteen healthy controls. MDD patients were divided by tertile based on Hamilton Rating Scale for Depression (HRSD) scores: mild to moderate depression (HRSD 14-19, n= 16), severe depression (HRSD 20-23, n= 19), and very severe depression (HRSD ≥ 24, n= 17). DTI scans were analyzed using the TBSS (Tract-Based Spatial Statistics) modules of the FMRIB Software Library (FSL) 5.0. This allowed for creation of an alignment-invariant map of the brain's white matter. These white matter maps were then used to train a linear SVM classifier to differentiate control from MDD patient scans, and differentiate HRSD tertiles. Results: Classification of DTI data using linear SVM showed statistically significant diagnostic classification of MDD and HC (AUROC 0.67) and in two HRSD tertiles vs. controls (AUROCs: mild to moderate, 0.67; severe 0.68), and in two comparisons within HRSD tertiles (AUROCs: mild-to-moderate vs. very severe, 0.64; severe vs. very severe, 0.68). Conclusions: Using TBSS-based white matter maps, the machine learning classifier achieved statistically significant classification of two MDD severities vs controls and two MDD severity comparisons, but there was no added value in diagnostic accuracy in the classification of MDD based on severity of symptoms.

Disclosures: J. Benoit: None. **M. Brown:** None. **A. Greenshaw:** None. **S. Dursun:** None. **R. Ramasubbu:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Astra-Zeneca.

Poster

830. Data Analysis: Human

Location: Hall A

Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 830.06/DD38

Topic: G.07. Data Analysis and Statistics

Support: This research was supported by a contract with the National Institute of Information and Communications Technology entitled, 'Development of network dynamics modeling methods for human brain data simulation systems'.

Title: Reproducibility and sensitivity analysis of MEG source current estimation

Authors: *Y. TAKEDA, D. LI, N. HIROE, M.-A. SATO, O. YAMASHITA;
ATR Neural Information Analysis Labs., Kyoto, Japan

Abstract: Source current estimation from MEG data is an ill-posed problem that requires prior assumption about brain activity. The reliability of estimated currents has been evaluated using simulated data with known true currents. For real MEG data, however, it is difficult to evaluate the reliability because true currents are unknown. Examining reproducibility across recording sessions could be a way to evaluate the reliability. However, it is not sufficient because imposing the strong prior assumption may increase the reproducibility. In this study, we propose a measure that combines the reproducibility and task sensitivity to evaluate the reliability of source currents estimated from real MEG data. For each vertex, this measure evaluates how large the difference of estimated currents across tasks is compared to the difference of estimated currents across sessions. We applied this measure to source currents estimated from MEG data during viewing motion stimuli. In two separate days, we conducted the same MEG experiment using visual motion stimuli at 0, 3.5, 7.0, 14 deg/sec. To obtain prior information about brain activity, we also conducted a fMRI experiment. From the MEG data, we estimated source currents in three ways: Variational Bayesian Multimodal EncephaloGraphy (VBMEG) with fMRI prior, VBMEG with uniform prior, and linearly constrained minimum variance (LCMV) beamformer. Our measure shows higher values for the source currents estimated by VBMEG with fMRI prior than those estimated by VBMEG with uniform prior and LCMV, indicating that using fMRI prior increase the reproducibility and sensitivity of the estimated source currents. From real MEG data, therefore, our measure confirms the validity of using fMRI prior in source current estimation.

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Poster

830. Data Analysis: Human

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Topic: G.07. Data Analysis and Statistics

Support: NIH Grant 5R90DA023426-09

Title: Multi-connection pattern analysis (MCPA): multivariate discriminant analysis of functional connectivity between neural populations

Authors: *Y. LI[1,3,2], A. S. GHUMAN[3,4];
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Abstract: How neural populations and interacting neural circuits encode information is a central question in neuroscience. Pattern classification methods from modern statistics and machine learning, such as multivariate pattern analysis (MVPA), have gained popularity in recent years for decoding the information content contained in neuroimaging and multiunit data. These methods allow one to go beyond examining the involvement of a population in a particular neural process and infer the representational content of the population activity. However, current MVPA methods do not allow one to assess the discriminant information encoded in the pattern of functional connections between different neural populations. Furthermore, traditional methods for assessing functional connectivity only allow one to examine differences in the degree of coupling across conditions and not the information carried by the pattern of interregional connections. Here we propose a method termed Multi-Connection Pattern Analysis (MCPA) to extract the discriminant information about cognitive states solely from the shared activity between neural populations from two brain areas. First, canonical correlation analysis (CCA) was used to learn the transformation of the activity between two populations. A classifier was then trained based on the patterns of interaction corresponding to different cognitive conditions. Simulation results showed that MCPA could successfully detect the information contained in the functional connectivity patterns across a wide range of simulated data types covering the normal range of neuroimaging and intracranial data from a variety of modalities. We then used MCPA to analyze intracranial EEG data recorded from human occipital face area (OFA) and fusiform face area (FFA) during a visual face processing task. The results demonstrated that the interaction between OFA and FFA contained category-level information about faces in an early time window (0-200 ms after stimulus onset), and information about which face the participant was viewing in a later window (after 200 ms). The timecourse of this interaction is consistent with a previous neural decoding study based on event related potential signals within only FFA, suggesting that face categorization and recognition relies on reciprocal OFA-FFA interactions. Here we present a novel tool that uses multivariate interactions between neural populations to decode representational content contained in the coupled activity of distributed, interacting neural circuits.

Disclosures: Y. Li: None. **A.S. Ghuman:** None.

Poster

830. Data Analysis: Human

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Time: Wednesday, October 21, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 830.08/DD40

Topic: G.07. Data Analysis and Statistics

Support: 1U54MH091657

Title: Magnetoencephalography analysis in the human connectome project (HCP)

Authors: *G. MICHALAREAS[1], F. DI POMPEO[2], J.-M. SCHOFFELEN[4], R. OOSTENVELD[5], S. DELLA PENNA[3], L. LARSON-PRIOR[6], L. MARZETTI[3], F. DE PASQUALE[3], M. KELSEY[7], A. BABAJANI-FEREMI[9], F. PRIOR[7], P. FRIES[1], V. PIZZELLA[3], G. ROMANI[3], M. CORBETTA[8], A. Z. SNYDER[8];
[1]Ernst Strüngmann Inst. (ESI) For Neurosci., Frankfurt Am Main, Germany; [2]Dept. of Neurosci. and Imaging and Inst. for Advanced Biomed. Technologies, Univ. G. D'Annunzio, C, Italy; [3]Univ. G. D'Annunzio, Chieti, Italy; [4]Max Planck Inst. for Psycholinguistics, Nijmegen, Netherlands; [5]Donders Inst. for Brain, Cognition and Behaviour, Radboud Univ. Nijmegen, Nijmegen, Netherlands; [6]Dept. of Radiological Sci., [7]Electronic Radiology Lab., [8]Dept. of Radiology, Washington Univ. Sch. of Med., St. Louis, MO; [9]Le Bonheur Children's Hosp., The Univ. of Tennessee, Memphis, TN

Abstract: The Human Connectome Project (HCP) aims at exploring and mapping consistently the anatomical and functional brain networks as well as their functional principles, their relation to behaviour and the role of the underlying genetic factors that regulate them. In the context of the HCP in the recent years, a large amount of high quality data from different modalities has been acquired. In terms of neuroimaging, Magnetic Resonance Imaging (sMRI, fMRI, DTI) has been used to study the topology of anatomical and functional connections with high-spatial resolution. Magnetoencephalography(MEG) has been used to study the dynamics of activity in and between frequency bands due to its very high temporal resolution. Most importantly this data in raw, preprocessed and processed formats is available to the whole community. In this work we present all the MEG analysis pipeline protocols and results that are disseminated to the scientific community from the HCP. In the HCP, MEG data was acquired during Resting State and 3 different Task experimental paradigms, aiming to reveal the functional networks of Motor Control, Working Memory and Language Processing. While during the Task experiments both evoked and induced activity are modulated by the characteristics of the exogenous stimulation, in the Resting State brain activity is intrinsically modulated. Accordingly, MEG data from Resting and Task experiments has different characteristics and this means that also different analysis approaches are better suited for these two types of paradigms. In both cases we investigate

connectivity in different frequency bands and in different time epochs in the source space using the preprocessed MEG data. The main connectivity metrics employed are band-limited power correlation and imaginary coherence metrics. These connectomes are produced in CIFTI format and can be handled through the Connectome Workbench, so that MEG connectomes can be related to the fMRI and DTI processed data of the HCP. In fact, the cortical sheet representation of the source space allows for comparison between different modalities by means of parcellation scheme. Pipelines released are mainly automatic and can be used to reproduce the results already released to HCP users, to process HCP data with different settings or to analyze different data. To our knowledge, this is the first time that a complete and unified set of processing tools, able to provide the user with a variety of frequency resolved MEG connectomes at different time and spatial scales, together with a large sample of already processed subjects have been delivered to the scientific community.

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Poster

830. Data Analysis: Human

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Program#/Poster#: 830.09/DD41

Topic: G.07. Data Analysis and Statistics

Title: Assessing the influence of color scales on data interpretation in neuroimaging - a comparative empirical study

Authors: ***M. CHRISTEN**[1], P. BRUGGER[3], S. I. FABRIKANT[2];
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Abstract: Objective: The visualization of complex data routinely relies on mapping data to a color space in order to display, for example, activity changes in functional neuroimaging. However, empirical research on how the mapping of data onto color space influences data interpretation is sparse. We empirically assessed the effect of using different color scales (rainbow, heated body, color-intensity change, red-white-blue) and the influence of image background (white/black) on the interpretation of data in neuroscience (imaging brain activity from normal brains to locked-in state, minimally conscious state, vegetative state up to brain

death) and in geography (depictions of environmental sustainability models in a country that match the employed brain state descriptions). Methods: The study used a between-group-design with pair-matched subjects regarding age, gender and imaging expertise (neuroimaging experts, geo-visualization experts, lay people; n=134 per group) where one out of eight conditions per paradigm (brain state, sustainability state) has been presented randomly to a single subject using a web-based survey. Additional question assessed issues like professional experience and image production practice. Results: We hypothesized that domain experts would be least influenced by a particular color scale when interpreting the depicted data, such as determining whether an image faithfully conveys the fact that a person is brain dead. We measured interpretation variability by taking the total mean over all conditions for a single state as reference and then by determining the distribution of differences per condition and group. Contrary to our hypothesis we found that neuroimaging experts' image interpretations were more strongly influenced by changes in color scales in both the neuroscience data and geo-data conditions, compared to the other participant groups. This interpretation difference was significant for neuroscience data depictions. We also found that trust in the visualized data depends on the valence of the depicted theme, for example, whether a healthy brain or non-healthy brain state is depicted. Interestingly, data depictions representing a negative state (i.e., brain death or "ecological death") are considered significantly more trustworthy if the image background is black. Conclusions: Given the importance of neuroimages and imaging software for conveying results in neuroscience, in particular in the public discourse, the study points to the need of generating increased awareness on the potential influence of data visualization methods on data interpretation, in particular also amongst the domain experts themselves.

Disclosures: **M. Christen:** None. **P. Brugger:** None. **S.I. Fabrikant:** None.

Poster

830. Data Analysis: Human

Location: Hall A

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Support: NICHD R01HD078561

NICHD R21HD069001

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NIH MH081896

Title: Asymmetry of neuronal migration pathways in developing human fetal brains

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Abstract: The radial glial pathway and ganglionic eminence (GE) are two major neuronal migration streams in humans, and have been investigated by histological assessment. However, due to limitations inherent to microscopic studies, only small regions can be investigated through histological assessment alone, and little evidence is available about their three dimensional fiber pathways throughout the entire brain. Therefore, we imaged and analyzed whole human brain radial pathways and the GE structure using high angular resolution diffusion MR imaging (HARDI) tractography. In this study, we imaged ten intact fixed fetal cerebral (17 gestational weeks (GW), 18 GW, 19 GW, three 20 GW, three 21 GW and 22 GW) and eight intact *in vivo* newborn cerebral (two 30 GW, 34 GW, 35 GW and four 40 GW). We statistically compared the GE and radial pathways in the left side and the right side of the brain, as well as radial pathways in the anterior and posterior regions of the brain. Two age groups (equal or younger than 22 GW and older than 22 GW) were separately analyzed to minimize confounding factors from the difference between *ex vivo* and *in vivo* imaging. The volume of radial pathways in the left hemisphere was significantly larger than that of the right hemisphere in the specimens equal or younger than 22 GW. The volume of posterior radial pathways was also larger than that of the anterior pathways. In contrast, no significant differences were observed in ages older than 22 GW. Moreover, our study did not identify any significant differences related to GE pathways. These results suggest that the two neuronal migration pathways regress in differential manners, and the duration of radial neuronal migration varies depending on brain regions, potentially allowing regionally various amounts of excitatory and inhibitory neurons migrate along the radial pathways.

Disclosures: Y. Miyazaki: None. **J.W. Song:** None. **E. Takahashi:** None.

Poster

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Research Council of Canada (NSERC)

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NEI R01EY017699

Title: Brain transfer for the analysis of cortical data

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Abstract: The cerebral cortex is the largest part of the human brain and is critical for a variety of sensory, cognitive, and motor functions. Though the functional and anatomical organization of cortex are related, the complexity and variability of the folds makes comparisons across individuals challenging. Neuroimaging often requires accurate algorithms for matching cortices. Efficient mathematical frameworks are consequently sought for analyzing data on inflated cortical surfaces, and for transfering corresponding anatomical and functional maps between subjects. Standard methods typically rely on anatomical features, including sulcal depth, to drive the alignment across individuals (Fischl et al. 1999). Recent methods can align subjects based on the similarity of neural activity patterns (Conroy et al. 2013). These present approaches typically treat each task separately and can be computationally expensive, requiring several hours to process a single subject. Here, we propose Brain Transfer, a spectral shape framework that provides fast point matching with confidence regions, and transfers of functional maps, within minutes of computation. Spectral methods have the advantage of capturing the underlying intrinsic geometry of shapes. We improved over previous spectral approaches by addressing the instabilities of geometrical harmonics (Lombaert et al. 2013). The improved normalization is key to process and analyze functional data on matched cortices. More precisely, our contributions consist of (1) the optimization of a spectral transformation matrix, which combines both, surface correspondence and normalization of geometrical harmonics, and (2) a localized spectral decomposition of functional data, via focused harmonics. This spectral transfer provides a robust formulation for spectral methods and naturally handles sign changes as well as differences across Laplacian eigenvectors. The novel focused harmonics capture the essentials of the intrinsic geometrical properties in a confidence area, and form a basis for reconstructing the shape of cortical surfaces and functional maps across subjects. Thus, Brain Transfer enables the transfer of functional data across interchangeable cortical surfaces, accounts for localized confidence, and gives a new way to perform statistics on surfaces. When matching cortical surfaces based on sulcal depth, we achieve similar accuracy in a fraction of the time compared to spherical-based methods. We outperform standard spherical-based methods when matching functional data within the visual cortex.

Disclosures: **H. Lombaert:** None. **M.J. Arcaro:** None. **S. Kastner:** None. **N. Ayache:** None.

Poster

830. Data Analysis: Human

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Program#/Poster#: 830.12/DD44

Topic: G.07. Data Analysis and Statistics

Title: Task-induced edge density as a marker for dynamic network formation in fMRI

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Abstract: The formation of transient networks in response to external stimuli or as a reflection of internal cognitive processes is a hallmark of human brain function. However, in the past twenty years, task-based fMRI studies have primarily focused on signal amplitude changes or connectivity related to a few selected nodes. Shifting focus away from signal amplitudes or constraining connectivity patterns of a few selected nodes, we propose an alternative view on fMRI data analysis by considering large-scale, task-induced synchronization networks. Networks consist of nodes and edges connecting them, where nodes in our method correspond to voxels in fMRI data, and the weight of an edge between any two voxels is determined via task-induced changes in dynamic synchronization between their respective times series. Based on these definitions, we developed a new data analysis algorithm that is designed to identify time series of voxels in an fMRI image that collectively synchronize in response to a task. At the heart of our approach is the concept of spatially localized and task-induced edge density motivating us to call this algorithm "TED" (Task induced Edge Density). In short, TED identifies edges in a brain network that differentially respond in unison to a task onset and that occur in dense packs of edges with similar responses to tasks. We found TED to be a very strong marker for dynamic network formation that easily lends itself to statistical analysis using large scale statistical approaches such as the local false discovery rate (local fdr). A major advantage of TED compared to other network-based methods is that it does not require a presegmentation of the data for dimensionality reduction as it can handle large networks consisting of tens of thousands of voxels. Because its conceptual basis is task-induced synchronization it does not depend on a

hemodynamic response model. We applied TED to task-based fMRI data provided by the Human Connectome Project focusing on the motor, social recognition and working memory tasks. In all cases, TED identified several task-specific, large-scale patterns of synchronization. We conclude that the new TED method provides us with an entirely new window into the immense complexity of human brain function.

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Poster

830. Data Analysis: Human

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Program#/Poster#: 830.13/DD45

Topic: G.07. Data Analysis and Statistics

Title: Heartbeat evokes electrical potential in human insular and cingulate cortex

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Abstract: Neural processing associated with interoceptive signals underlies maintenance of homeostasis and also could impact cognitive functions such as emotion, memory, and perception. Neural response associated with heartbeat could be investigated by analyzing heartbeat evoked potential (HEP). HEP has been associated with heartbeat awareness ability, pain perception, empathy, and visual perception. However, two important questions are still unanswered in the HEP literature. First, there is no direct evidence showing HEP is truly 'evoked' neural activity rather than reflecting mere heart cycle related artifact such as cardiac field artifact or pulse artifact. Second, cortical and subcortical source of HEP is still unknown. Although a recent ECoG study showed HEP can be measured from the somatosensory cortex, it is missing whether HEP can be directly recorded in the alleged interoceptive cortex, such as insula and cingulate cortex. To answer these questions, we analyzed HEP using subdural strip electrodes including both insula and cingulate cortex location from 2 epileptic patients while patients were lying in the bed without any experimental task. In order to test whether HEP is truly evoked neural response, we analyzed inter-trial coherence (ITC) of HEP. On both patients, we observed transient increase of ITC at 6 Hz around 200ms after the onset of R-peak from electrodes place in the insula and cingulate cortex. Across 2 patients 35% of tested electrodes showed significant ITC increase after the onset of R-peak. Our findings represent a compelling evidence that HEP reflects truly 'evoked' neural activity, and is not an electrophysiological

artifact associated with the heart cycle related activity. Indeed the finding of transient increase of ITC selectively after the onset of R-peak indicates heartbeat evokes transient neural activity from specific brain areas. Furthermore increased ITC was mainly observed in alleged interoceptive cortex such as insula and cingulate cortex. This finding reveals that insula and cingulate cortex in humans processes neural activity associated with visceral interoceptive signals as shown in animal studies.

Disclosures: H. Park: None. **O. Blanke:** None.

Poster

830. Data Analysis: Human

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Support: Alberta Health Services Grant

Alberta School of Business Pearson Faculty Fellowship

Title: Estimating whole brain connectivity dynamics using spectral clustering

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Abstract: A great challenge in neuroscience is reconstructing and understanding the dynamic manner in which brain regions interact with one another in both task-based and resting-state brain imaging studies. To understand precisely how such complex brain networks evolve under varying experimental and/or behavioral conditions could have a major impact on our comprehension of the functional organization of the brain. Recently, the use of graphical models for estimating the functional connectivity or brain networks has become increasingly popular. In most functional magnetic resonance imaging (fMRI) studies, the networks between brain regions are assumed to remain fixed or static over the course of the experiment. However, there is now more evidence that the network or functional connectivity is changing over time even when the subjects are at rest. In this work, we first introduce a novel time-varying statistical method that dynamically clusters brain regions or voxels by their functional connectivity. This new method allows for situations where the number of brain regions is greater than the number of time points in the experimental time course ($n < p$). Hence, this method promises to offer deeper insight into the mechanisms of the brain as it can be used for the dynamic modelling of a very large number

of voxels or brain regions. We also propose a new nonparametric method for estimating time varying graphical structures, or networks between brain regions, that allows for both smoothly changing graphs over time and also abrupt changes in the brain network structure. The method is very flexible as there is no a priori assumption on where the changes occur. This new method has a major advantage over moving window-type methods as we do not have to choose the window length. We apply both new methods to simulated data and to a resting-state fMRI data set. For the fMRI data set, participants are instructed to rest in the scanner for 9.5 min, with the instruction to keep their eyes open for the duration of the scan. The individual time series data are bandpass-filtered and motion corrected. The voxel time courses at white-matter and CSF locations are submitted to a Principal Components Analysis and, together with the motion parameters, we use all components with an eigenvalue > 1 as independent variables in a subsequent nuisance regression. Each voxel's time series is residualized with respect to those independent variables. The residual time series images are then smoothed with an isotropic Gaussian kernel (FWHM=6mm). We apply the Automated Anatomic Atlas Labeling to the adjusted voxel-wise time series and produce time series for 116 ROIs for each subject.

Disclosures: I. Cribben: None.

Poster

830. Data Analysis: Human

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Topic: G.07. Data Analysis and Statistics

Support: DFG GA 730/3-1

DLR BCCN 01GQ1004A

Title: Some overlooked properties of cross-validated classification and the implications for hypothesis testing in life science data

Authors: *H. JAMALABADI[1,2,3], S. ALIZADEH[1,2,3], M. SCHÖNAUER[1,3,4], C. LEIBOLD[5,3], S. GAIS[1,3,4];
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Abstract: Recently, multivariate pattern classification (MVPC) has come into widespread use in various neuroscience areas for decoding and hypothesis testing. However, although it is often used as a replacement of parametric statistics, its behavior is not well understood and is often used without a clear understanding of its intricacies.To investigate reliability of applying MVPC for hypothesis testing purposes, we explored the properties of cross-validated classification in low sample size, low effect size data (LSS-LES) data, which is typical in the life sciences.To describe the distribution of classification results we usedan analytical approach and simulations when systematically varying sample size, effect size, and number of cross-validation folds in a cross-validated classification scheme. For our simulations we used synthetically generated as well as real EEG data. The recorded EEG data comprises event related potentials (ERP) elicited by two kinds of visual stimuli in a visual learning task. We show that cross-validated MVPC behaves unexpectedly in LSS-LES data: correct classification rates (CCRs) are non-binomially and asymmetrically distributed in case of no or low effect size. Distributions exhibit strong skewness and a high probability for classification rates below what should be expected from chance classification. In the one-dimensional case, we analytically prove that below-chance classification rates must occur in cross-validationin LSS-LES data, because of the dependency between subsample means. The skewed distribution of classification rates has strong implications when using MVPC for hypothesis testing. It can lead to far below-chance classification rates as well as to a higher number of spuriously high CCRs than expected. In particular, below-chance outcomes must not be discarded as experimental failures or outliers, but regarded as part of the expected distribution of results. Our analyses also warrant the conclusion that CCRs do not reflect the size of the effect under investigation nor the classifier's sensitivity. We conclude that effect sizes should be reported in terms of significance levels and estimated using randomization tests. Sensitivity of the classifier should be reported in terms of statistical power. Finally, in simulations, we show that cross-validation procedures using a low number of folds, e.g. 2-fold, are generally more sensitive, i.e. have higher significance, than those obtained using a higher number of folds, even though the average CCRs are often considerably lower.

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Poster

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Down Syndrome Research Foundation (Burnaby, BC, Canada)

Title: Revised minimum variance beamformer weights for functional brain imaging data analysis

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Abstract: Adaptive minimum variance beamformers are widely used source-localization analysis tools for functional magnetoencephalography (MEG) and electroencephalography (EEG) brain imaging data. When the target brain activity presents itself in the form of spatially localized responses, the procedure usually involves two steps. First, positions and orientations of the sources of interest are determined. Second, the filter weights are calculated and source time courses reconstructed. This last step is the focus of the current study. Despite different approaches utilized at the source localization stage, basic expressions for the weights have the same form, dictated by the minimum variance condition. These classic expressions involve covariance matrix of the measured field, which includes contributions from both the sources of interest and the noise background. In this study, we present analytical evidence that the weights used in conventional beamformer analysis could alternatively be obtained, if full covariance is replaced with the noise covariance, provided the target lead fields exactly match the lead fields of the true sources. In practice, however, localization and modeling errors are always present and certain mismatch is inevitable. We show that such mismatch results in partial suppression of the true sources because by design the beamformer tries to cancel interference to the target. To avoid this effect, the “alternative” weights constructed using the noise covariance matrix should be

used. Our analytical results demonstrate that such weights provide in many situations better reconstruction quality than the traditional ones. We further demonstrate in simulations and in human MEG measurements that alternative weights a) yield better source-level signal-noise ratio (SNR) and more accurately reconstructed waveforms b) provide more precise estimates of inter-source correlations c) decrease adverse effects of the source correlations on the beamformer performance for commonly used single-source beamformers. Most importantly, using the alternative weights comes at no additional computational cost, as the weights expressions remain essentially the same, while the scientific outcome is poised to increase by improving source-based analysis and connectivity dynamics of functional EEG and MEG data.

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Poster

830. Data Analysis: Human

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Weston Brain Institute

Michael J. Fox Foundation for Parkinson's Research

Alzheimer's Society

Brain Canada

Title: Towards a complete volumetric assessment of the human memory circuit: Segmentation of medial temporal lobe, and subicular cortices on high-resolution 3T images

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Montreal, QC, Canada; [6]Inst. of Biomaterials and Biomed. Engin., Univ. of Toronto, Toronto, ON, Canada

Abstract: INTRODUCTION The human memory circuit begins with inputs to the perirhinal cortex (PRC), and parahippocampal cortex (PHC). Incoming information is re-routed to the entorhinal cortex (ERC) before entering the hippocampus (HC) via the perforant pathway. From the HC, white matter projections lead out of the medial temporal lobe (MTL) via the fornix to higher cortical regions. Our aim was to create a detailed, anatomically-accurate protocol for the segmentation of all MTL and subicular cortices on magnetic resonance (MR) images that would also complement our previous HC subfield and white matter atlases. METHODS T1- and T2-weighted high-resolution MR images were acquired for 5 healthy controls (mean age=37 years; 0.3 mm isotropic voxel dimensions) on a 3T GE scanner. Manual tracing was completed using MINC Display while employing a tri-planar segmentation approach. In addition, 3D reconstructions were used to aid segmentation in areas of obscurity. Given the inherent homogeneity present along the grey matter of the MTL cortices, reliable definitions based on contrast differences were relatively nonexistent. Therefore, the use of geometric borders adhering to the underlying anatomy were employed where possible. Multiple print, MR, and histological atlases, as well as existing publications outlining MTL anatomy were used in protocol development. RESULTS The present segmentation protocol identifies the PRC, ERC and PHC in their full anterior to posterior extent. The protocol also enables identification of both the presubiculum and parasubiculum and is tailored to compliment both the Winterburn et al. (2015) HC subfield atlas, and the Amaral et al. (in prep) extra-HC white matter atlas (See Figure 1 for protocol details). CONCLUSION Here we present a comprehensive and anatomically accurate protocol for the volumetric assessment of the MTL and subicular cortices. Given its close fit with the other available protocols from our group, their combined use can enable a more in-depth volumetric characterization of the memory circuit in various populations and disease states.

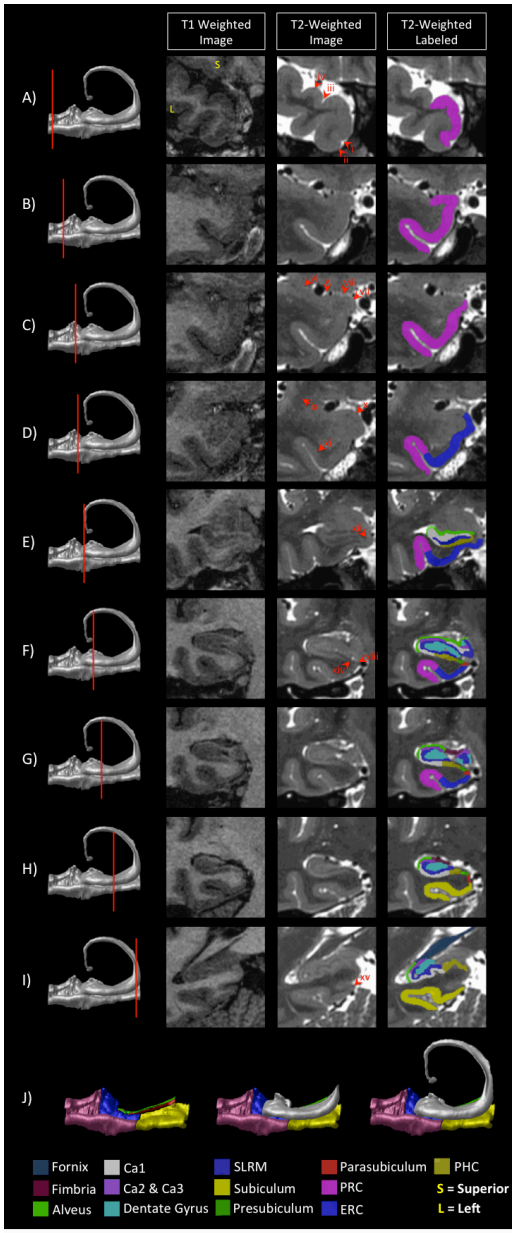

Figure 1. Sample of segmentation protocol for left medial temporal lobe (MTL) cortices. Rows A-I depict coronal sections of T1 and T2-weighted images. An additional column includes completed MTL tracings on T2-weighted images with both the Winterburn et al. (2013) subfield and Amaral et al. (in prep) hippocampal white matter atlases overlaid. 3D renderings depict the level at which each coronal slice occurs within the sagittal length of the MTL (red line). **A:** Depicts a coronal section through the anterior extremity of the MTL. Tracing of the perirhinal cortex (PRC) begins at the first slice which the collateral sulcus is visible (i). In these slices and subsequent, the inferolateral border of the PRC is the elbow of where the grey matter of the collateral sulcus comes to meet the inferotemporal cortex (ii). The hyperintense signal of the grey matter ribbon is followed superiorly until the fundus of the temporopolar sulcus (iii). The grey matter of the gyrus of Schwalbe (iv) is not included as PRC. **B:** Row depicts tracing protocol anterior sections through the MTL. The same inferomedial and superiomedial borders are maintained. At this point the fundus of the collateral sulcus typically begins to increase in depth and the temporopolar sulcus begins to stretch and subsequently takes a flattened appearance. **C:** At more posterior sections of the MTL, the limen insulae begins to form (v) as the grey matter ribbons of the planum porale and the piriform cortex begin to merge (vi). Here the the superior boundary of the PRC incudes all gray matter until the elbow of the uncus (vii) prior to the sulcus semiannularis (viii). **D:** Row depicts coronal section at the level of the frontal temporal junction (FTJ). As soon as the FTJ appears (ix) the entorhinal cortex (ERC) begins to be traced. The superior border of the ERC follows the same demarcation as the PRC in pervious slices (x). The inferior border of the ERC extends half way down to the fundus of the collateral sulcus (xi) and borders the PRC. The inferiolateral border of the PRC remains the same. **E:** Row depicts coronal sections at the level of the extreme anterior head of the hippocampus. The same inferior and superior boundaries for the PRC and ERC remain. Here, the ERC extends superiorly half way up the uncus (xii). **F:** Row depicts level of the middle hippocampal head. Once the grey matter ribbon of the ERC rises to meet the subiculum of the hippocampus the presubiculum and parasubiculum are traced. First, a line is placed at the bend of the hippocampal gyrus where the uncual sulcus opens to meet the cerebrospinal fluid of the lateral ventricle (xiii). The existing curve is intersected into two parts. The presubiculum extends superiorly half way up the bend (xiv) to reach the subiculum, while the parasubiculum extends inferiorly half way down the bend to meet the ERC. **G:** Posterior slices through the hippocampal head depicting a disappearing uncus. Moving more posteriorly, segmentation of the ERC, PRC and the pre/parasubiculum maintain the same rules. **H:** Coronal slice through the body of the hippocampus. Once the uncus disappears from the medial area adjacent to the hippocampal head, the PRC and ERC are no longer traced. Instead the entire cortex is traced as parahippocampal cortex (PHC; following the same inferiolateral and superiomedial borders as before). **I:** Coronal section through the level of the hippocampal tail. Tracing guidelines for the PHC remain the same, however, the medial extent terminates just prior to the opening of the anterior calcarine sulcus (xv). **J:** 3D reconstruction of MTL segmentation protocol product, followed by MTL atlas overlaid with Winterburn et al. (2013) subfield segmentation and Amaral et al. (in prep) hippocampal white matter atlas.

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Poster

830. Data Analysis: Human

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Support: DFG GA730/3-1

DLR BCCN 01GQ1004A

Title: Decoding continuous EEG signals during sleep using an ensemble of support vector machines

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Abstract: Recent advances in multivariate pattern classification (MVPC) methods have made it possible to investigate covert cognitive processes in continuous brain activity. These methods can help to determine whether specific information is present in electroencephalography (EEG) without requiring precise hypothesis about localization and timing of the signal, assumption of statistical normality, or arbitrary significance thresholds. In this study, we employed MVPC to see whether human sleep EEG contains any information about what has been learned before sleep. This is of particular interest because animal and human imaging studies support the hypothesis that the brain reprocesses previously learned information during sleep (Wilson and McNaughton, 1994; Peigneux et al., 2004). It should therefore be possible to distinguish between EEG recordings from nights that were preceded by different learning situations. To detect such replay activity, we had 32 subjects learn pictures either of faces or of houses before an 8-h period of nighttime sleep. Brain activity was recorded with high-density EEG during a whole night of sleep. Our goal was to determine based on electrical brain activity during sleep what type of images (face/house) participants had viewed in the previous learning session. However, the large variability of EEG recordings from different subjects, high dimensionality of the recorded data (128 channels, 1 KHz sampling rate) and low sample size (32 subjects), posed specific problems for conventional MVPC algorithms. To address these problems, we developed a stepwise classification procedure based on a chain of linear support vector machine (SVM) classifiers. The main idea was to use the spatial and temporal features in two successive stages that could serve as a feature reduction method and at the same time increase the signal-to-noise ratio. We

find significant and generalizable learning-related processing in the EEG in all sleep stages, which occurs during specific time windows (2 and 5 hours after sleep onset) and which also correlates with later recall performance. We track the reprocessing in both rapid eye movement (REM) and non-REM (NREM) sleep but its spatial distribution over the scalp and its frequency composition differ between NREM and REM sleep. Interestingly, reprocessing in both sleep stages is cyclic in nature, and may be timed to windows of maximal synaptic efficacy. We showed that it is possible to classify long continuous EEG data recorded from sleep. Our proposed algorithm not only could be used to decode the content of sleep EEG but also to localize brain spatiotemporal electrical activity during sleep.

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Poster

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AivoAALTO project of Aalto University

Academy of Finland

Title: SumLog and order statistics for group-fMRI analysis

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Abstract: Introduction Parametric statistical tests, traditionally used in fMRI data analysis, rely on several assumptions that might not hold, such as normality of the underlying data. Violation of the assumptions may lead to biased inferences. In contrast, non-parametric approaches, such as the permutation test, make only minimal assumptions but are often computationally more expensive. We present order statistics and SumLog, a new, computationally efficient, non-parametric method, for group-fMRI analysis. **Methods** *Order statistics and SumLog* The voxel values (e.g. correlation or general linear model beta values) are sorted within subject and replaced by their ordinal numbers, which are then transformed into standard uniform variables. For *n*th order statistics, these standard uniform values are then ordered across subjects and the *n*th largest value is picked for each voxel. For SumLog, the

standard uniform variables are log-transformed and summed over subjects for each voxel. The values in the resulting single volume can be compared against theoretical thresholds from the beta (for order statistics) or gamma (for SumLog) distribution. *Simulation* We used a simulated 2D data set to test the performance of SumLog and order statistics, and to compare them with t-test and permutation test. Each subject's data comprised a 128 x 128 pixel image with a 100-point time course for each pixel. A source with one-period sinusoid time course was located at the center of the image. Subject count, noise level, co-registration accuracy, extent of spatial smoothing, and the between-subject variance in signal strength were varied. **Results** For most of the tested parameter combinations, the receiver operating characteristics (ROC) curve of SumLog was superior to the others. In general, SumLog gave equally many or more true positives than the other methods. The performances of the t-test and permutation test decreased drastically when the location of the active area varied across subjects. SumLog was over 6 000 times faster to compute than the permutation test. **Conclusions** SumLog was more resilient to noise and variability in signal location and strength than the other methods. It performed well even without smoothing and with low number of subjects (under 20). Compared with the permutation approach, SumLog was computationally much more efficient.

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Poster

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JSPS KAKENHI Grant Number 15K16011

Tateishi science and technology foundation

Title: Reconstruction of target velocity for overt/covert visual pursuit by using cortical currents estimated from MEG data

Authors: *K.-I. MORISHIGE[1,2], N. HIROE[2], M.-A. SATO[2], M. KAWATO[3];
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Abstract: The mechanism of prediction is necessary for realizing human smooth pursuit eye movements. Some cortical regions are well known for contributing to realize it, but it is not clear yet how the brain represents the spatial-temporal information for the eye movements. To answer such question, we measured MEG data during overt/covert pursuit tasks. Subjects were required to overtly or covertly pursue the target motion, that moves in the horizontal plane. Target motions were sinusoidal, and their frequencies were 0.5Hz and 0.8Hz. The cortical currents were estimated using a hierarchical Bayesian MEG inverse method (VBMEG), and investigated the spatial-temporal pattern of the currents. The measurement of MEG signals is contaminated by large magnetic artifacts stemming from eye movements, heart-beats, and so on. These artifacts can be of orders of magnitude larger than those of typical brain signals, thus making cortical current estimation extremely difficult. In order to remove the eye and heart-beat artifacts, we used extra-dipole method, which is based on hierarchical Bayesian method and simultaneously estimates the cortical and extra-brain source currents while placing dipoles not only on cortical surfaces but also on extra-brain sources. We calculated the current intensities from the estimated mean cortical currents during all tasks. The current intensities were increased in the cortical regions of the lateral occipital temporal cortex (LOTC), the intraparietal cortex (IPC), the precentral cortex (PreCC), and the medial superior frontal cortex (MSFC). These areas are related to the saccadic and smooth pursuit eye movements, and also activated when subjects orient their attention to visually target motion and pursue it covertly within their visual fields. The estimated cortical currents exhibited reasonable spatial-temporal patterns. We reconstructed the target velocities from the estimated cortical currents using a sparse regression method. Test datasets demonstrated a high similarity and an adequate fit between true and reconstructed target velocities (Pearson correlation coefficients: [overt 0.5 Hz] 0.95±0.01, [overt 0.8 Hz] 0.96±0.01, [covert 0.5 Hz] 0.87±0.06, [covert 0.8 Hz] 0.89±0.05; Goodness-of-fit: [overt 0.5 Hz] 0.76±0.07, [overt 0.8 Hz] 0.78±0.04, [covert 0.5 Hz] 0.33±0.09, [covert 0.8 Hz] 0.38±0.14), and weight values were mainly distributed on the LOTC. These results indicated that this cortical area plays a major role for realizing overt/covert pursuit tasks to represent the spatial-temporal information of the target velocities.

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Poster

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Topic: G.07. Data Analysis and Statistics

Title: Visualization of bicoherence for real-time signal processing and its practical application

Authors: ***K.-H. CHOI**, J. KIM, S. CHO, M. KIM, Y. SHIN, O. KWON, S.-Y. KANG, S. YEON, Y. RYU;
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Abstract: In this thesis, a novel signal processing tool is introduced which is visualization of bicoherence. The bicoherence is a measure for quantifying the extent of phase coupling in a signal and generally utilized for analyzing electroencephalogram in depth of anesthesia area. Although the bicoherence is a powerful measurement method, it is hard for human to catch the implicit meaning of that especially in case of real-time analysis. Here we visualized the bicoherence by a color. The method is following: 1) divide frequency range into two; 2) R(red) value is taken by bicoherence of F1~F2, F1~F2 be G(green) value, and F2~F2 be B(blue) value; 3) all value is averaged and normalized. As a result, we archive colors as the number of channels. To verify the efficiency of the proposed tool, we analyzed 64 channel electroencephalogram data. The experiment was for ensuring the effects on somatic nervous system caused by the acupuncture stimulation. The analysis by tool showed a trend that the colors obtained are lowered after manual acupuncture stimulation. The physiological significance of bicoherence index is not yet clarified. However, the contribution of the proposed tool is that it help to find out the meaning visually without further complex analysis. In the foreseeable future, this tool can be utilized in various real-time signal processing fields.

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Poster

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Title: Decoding cognitive states with a hidden Markov model

Authors: ***A. FLOREN**[1], B. NAYLOR[1], R. MIIKKULAINEN[1], D. RESS[2];
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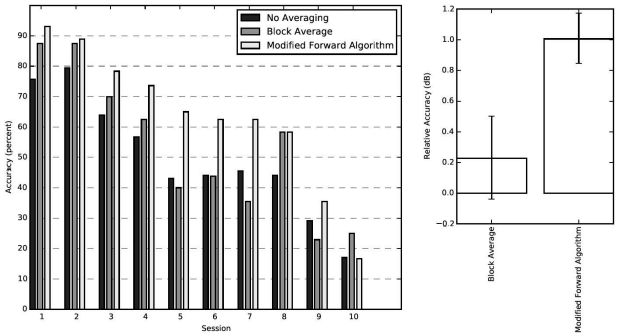
Abstract: Recent studies have shown it is possible to decode cognitive states from fMRI data. Decoding cognitive states could be useful for training and therapy applications by providing information about the participant's decision-making process. To overcome the low BOLD signal-to-noise ratio in standard neuroscientific experiments, block averaging is typically employed. However, the subject is not likely to switch between cognitive states in a simple block structure during a training or therapy exercise. Instead, we treat the series of cognitive states as a hidden Markov model (HMM) with the fMRI data as the observable variables. **Methods:** The forward algorithm can efficiently determine the most likely hidden state (X_t) given the sequence of observed variables (Y_1 to Y_t) in a HMM. We present a modified forward algorithm where we calculate $P(Y_t \mid X_t)$ by applying Baye's rule to a neural network (NN) approximation of $P(X_t \mid Y_t)$ and a Gaussian approximation of $P(Y_t)$. We tested our modified forward algorithm on a block-structured stimulus design so that we could compare it with block averaging. Subjects (N = 5 ,,2 sessions each) passively viewed a realistic virtual environment with animated characters. The number of characters varied (1—6) in a 15-s block structure. 12 blocks were presented in each run, and 4—6 runs were presented in each session. Whole-brain fMRI data was collected on a 3T scanner with 2.5-mm cubic voxels and TR=2.5 s, using 2x GRAPPA acceleration. The modified forward algorithm was applied to the fMRI data to decode the number of characters. NNs were also trained on the fMRI data and block averaged data for comparison. **Results:** For all subjects and all sessions, the modified forward algorithm shows a significant increase in decoding accuracy over simple block averaging and baseline NN performance. **Discussion:** The modified forward algorithm significantly outperforms simple block averaging without imposing a block structure on the stimulus. This allows for improved decoding accuracy of cognitive states during more natural tasks and potentially during training and therapy exercises.



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Poster

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Title: Mapping dorsal and ventral caudate in humans

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Abstract: Caudate nuclei are subcortical gray matter structures that can be divided into dorsal and ventral regions based on associated connectivity and functions. Autopsy and lesion studies suggest that the dorsal region is associated with executive functions such as working memory and reasoning, while the ventral region is implicated in moresomatic symptoms. Novel processing approaches may help to improve the mapping of caudate ventral/dorsal boundaries. The goal of this work is to examine whether resting-state fMRI data can be used to validly differentiate dorsal from ventral regions. We recorded resting state fMRI data from 56 non-demented old adults (age: 69.07±5.92 years; MMSE/MOCA: 26.07±2.68) who also completed cognitive testing for working memory (WMS-III Letter Number Sequencing, Digit Span), reasoning, pain (Brief Pain Inventory), and fatigue (BFI). To segment dorsal and ventral regions, we generated caudate voxels whole brain correlation maps. A K-means clustering analysis with K=2 yielded a dorsal caudate map and a ventral caudate map consistent with anatomically determined dorsal/ventral parcellation. We then applied functional connectivity analysis to examine the hypothesized dorsal/ventral caudate-cortex interaction patterns and expected dissociations between dorsal/ventral caudate functions by correlating caudate-cortex functional connectivity with neuropsychological test scores. Results identified dorsal caudate-cortex functional connectivity positively associated with working memory index and fluid reasoning scores, while ventral caudate-cortex functional connectivity associated with pain, fatigue severity, and anxiety. This study demonstrates the validity of fMRI methods for segmenting dorsal and ventral regions with the caudate nucleus in non-demented older adults.

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Topic: G.07. Data Analysis and Statistics

Title: Attenuation correction of PET data in hybrid MR/PET scanners: Performance of CT-based versus template-based approaches

Authors: E. ROTA KOPS[1], *H. HAUTZEL[2], G. ANTOCH[3], C. LERCHE[1], H.-W. MÜLLER[4], N. J. SHAH[1];
[1]Inst. of Neurosci. and Med. 4, Forschungszentrum Jülich, Jülich, Germany; [2]Forschungszentrum Jülich & HHU Düsseldorf, Med., Jülich, Germany; [3]Dept. of Diagnos. and Interventional Radiology, Heinrich-Heine-University Düsseldorf, Med. Fac., Düsseldorf, Düsseldorf, Germany; [4]Dept. of Nuclear Med., Heinrich-Heine-University Düsseldorf, Med. Fac., Düsseldorf, Germany

Abstract: Aim: Attenuation correction (AC) of cerebral PET is a pre-requisite to achieve semi-quantitative or quantitative data. In PET/CT scanners the CT data are used for this purpose. However, AC in hybrid MR/PET scanners remains challenging. One way to overcome this are template-based attenuation maps (AMTmpl) derived by PET transmission scans using rotating 68-Ge/68-Ga sources. Here, we aim to compare the template-based and CT-based AC methods and the impact of these different methods on reconstructed PET images of the brain. Methods: 11 subjects underwent 18FDG MR/PET imaging and a whole head CT scan at the same day. The CT images were transformed to CT-based attenuation maps and filtered with 3 mm (AMCT3mm; resembling MR/PET resolution) and 9 mm (AMCT9mm; resembling AMTmpl resolution) filter width. The AMCT3mm served as reference. Comparisons between the attenuation maps were performed by using Dice coefficients D and by calculating true positive, true negative and false negative voxels. The 18FDG MR/PET emission data were reconstructed with the three AMs, then scaled to standardized uptake values (SUVs) and normalized to the MNI brain for using the AAL-VOI Atlas analysis. Correlation plots with regression equation, coefficients of determination R2 and relative differences (RD) between AMCT3mm and the other two AMs were derived. Results: As compared to AMCT3mm 91.8±2.4 % voxels were true positive for AMCT9mm (Dbone 0.82±0.04; Dsoft tissue 0.94±0.02; Dair 0.95±0.00) and 79.2±7.5 % for AMTmpl (Dbone 0.63±0.08; Dsoft tissue 0.83±0.08 and Dair 0.79±0.04). A misclassification of bone as soft tissue and vice versa was evident in both comparisons. The correlation plots of all VOIs in all patients revealed an R2mean of 0.992 for AMCT9mm and an R2mean of 0.964 for AMTmpl. For AMCT9mm an RDmean of 1.33±0.95 % (min=-0.12 %, max=2.85 %) and for AMTmpl an RDmean of 0.32±2.89 % (min=-4.74 %, max=5.43 %) were found. Conclusions: The template-based AC method shows considerable differences in comparison to the higher resolution CT-based AM with respect to the Dice coefficients, in particular in the classification of bone and soft tissue. While the resulting overall difference after

reconstruction of the 18FDG PET data remains small in some VOIs SUVs were under- or overestimated up to 5%.

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Poster

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Title: Information theory reveals neural correlates of predictions - a magnetoencephalography study

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Abstract: The theory that “predictive coding” is a fundamental functional principle of the brain has become increasingly popular in neuroscience. It suggests that the brain exploits information from context and memory for generating predictions in order to anticipate the incoming sensory evidence. Although this concept has been strengthened in many theoretical studies during the last decade, neurophysiological evidence for prediction signals in the brain remains rare. This is closely related to the fact that associating neural signals with prediction signals has not been easily possible. To solve this problem we suggest to identify prediction signals based on their predictability: Typically, predictions have to be maintained as the brain will not know when they are needed. If content is maintained and if there is a neural coding of this content then maintenance of predictions means that at least some property of the past signal should also predict the future signal. This predictability can be measured by an information-theoretic measure called active information storage (AIS), which quantifies the amount of stored information used for computation of the next processing step. We tested the ability of AIS to identify brain signals that are more predictable under specific task instructions. For this purpose subjects were presented with degraded pictures of faces and houses combined with task instructions alternating in 7 min blocks ("face or not?” or “house or not?”) in a discrimination

task during MEG recordings. This aimed at inducing predictions maintained for several minutes at distinct brain areas, supposed to be represented in more predictable brain signals for face or house instructions, respectively. We analysed 478 potential brain areas of 42 subjects in the prestimulus interval of the discrimination task and found higher AIS values in the inferior temporal gyrus/FFA and V1 when subjects maintained face information in memory. Thus, we demonstrate that the instruction to detect faces leads to higher AIS values in well-known face processing areas in the brain. This is in line with the assumption that face predictions are maintained in these areas. Spectral analysis at the identified brain areas revealed increased power in the beta frequency band when subjects were instructed to identify faces. Notably, beta frequencies have been linked to the representation of predictions in recent neurophysiological accounts of predictive coding. Thus, our results not only strongly indicate that AIS is an useful tool to analyse predictions in the brain, they also provide evidence for the assumption that neural activity in beta frequencies is related to the maintenance of predictions.

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